National Library
of Canada

Canadian Theses Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale
du Canada

Services des thèses canadiennes

CANADIAN THESES

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

THÈSES CANADIENNES

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30.

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

NL-339 (r.86/06)

Canada

THE UNIVERSITY OF ALBERTA

ON THE SYNTHESIS OF WARBURGANAL AND MUZIGADIAL

by

© FRANCISCO XAVIER TALAMAS

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING 1987

Permission has been granted to the National Library of Canada to microfilm this thesis and to lend or sell copies of the film.

The author (copyright owner) has reserved other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without his/her written permission.

L'autorisation a été accordée à la Bibliothèque nationale du Canada de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur (titulaire du droit d'auteur) se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation écrite.

ISBN 0-315-37675-9

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR FRANCISCO XAVIER TALAMAS

TITLE OF THESIS ON THE SYNTHESIS OF WARBURGANAL AND MUZIGADIAL

DEGREE FOR WHICH THESIS WAS PRESENTED DOCTOR OF PHILOSOPHY

YEAR THIS DEGREE GRANTED 1987

Permission is hereby granted to THE UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed)

PERMANENT ADDRESS:

Lirios #338
Col. Torreón Jardin
Torreón, Coahuila, México
CP 27200

DATED 19th JANUARY 1987

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled ON THE SYNTHESIS OF WARBURGANAL AND MUZIGADIAL submitted by FRANCISCO XAVIER TALAMAS in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY

W.A. Ayer (Supervisor)

J.W. Lown

J.W. Lown

W.A.G. Graham

H.J. Liu

E.E. Knaus

E.E. Knaus

Z. Valenta

Z. Valenta (External Examiner)

DATE 19th JANUARY / 1987

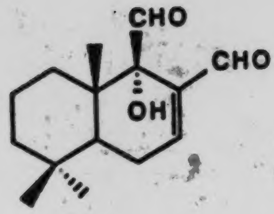
TO MY MOTHER

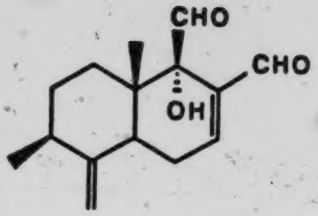
ABSTRACT

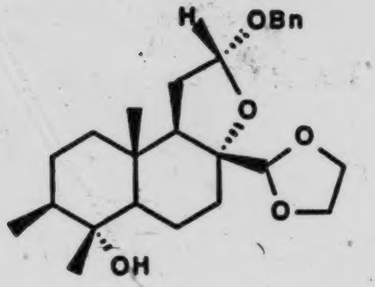
The sesquiterpenes warburganal (**1**) and muzigadial (**2**) are isolated from the bark of the East African tree Warburgia ugandensis. These two compounds display an interesting biological profile.

In this thesis we describe the synthesis of optically pure warburganal (**1**) using the resin acid levopimaric acid (**17**) as starting material. This transformation was carried out by removal of the top "isoprene unit" in several steps and modification of ring B to introduce the hydroxyaldehyde enal functionalities. Conversion of the C-4 carboxylate group to a methyl group was accomplished in two different ways from one of the intermediates in the synthesis.

The synthesis of compound **100-β** is also described. Hemiacetal **45**, one of the intermediates in the synthesis of warburganal (**1**), was used to carry out the skeletal transformations in ring A using the C-4 carboxylate group as the entry for the required modifications. Alcohol **100-β** is an attractive intermediate towards the synthesis of muzigadial (**2**) since it contains the C-3 β-methyl group and a masked exocyclic olefin at C-4.


1


2


100-β

ACKNOWLEDGEMENTS

- Professor W.A. Ayer for his help, guidance, and support during the course of this work.

- Dr. L.M. Browne for her invaluable help in the editing of this thesis.

- Dr. D. Ward and Dr. A. Shariff for many valuable discussions.

- The technical staff of the Department of Chemistry.

- The Alberta Heritage Foundation for Medical Research for financial support.

- Miss J.S. Racok for proofreading this manuscript.

- Miss A. Wiseman for typing the manuscript.

TABLE OF CONTENTS

CHAPTER PAGE

1. INTRODUCTION.. 1

2. RESULTS AND DISCUSSION.............................. 13

   1. Transformation of the Abietane Skeleton to the Drimane Skeleton.................... 13

   2. Synthesis of 4α-Methoxycarbonylwarburganal (**20**)......................... 34

   3. Reduction of the Carboxyl Group to a Methyl Group: Synthesis of Warburganal (**1**)........ 47

   4. Ring A Transformations: Towards the Synthesis of Muzigadial (**2**)................. 60

3. CONCLUSIONS... 90

4. EXPERIMENTAL.. 96

*****

REFERENCES.. 197

LIST OF FIGURES

FIGURE PAGE

1. Partial Newman projection of 38 and 39........ 23

2. 1- and 2-*trans*-octalin......................... 37

3. Hydroxyepoxide.................................. 68

4. Conformation of 100-α........................... 85

LIST OF SCHEMES

SCHEME PAGE

I. Ohno's synthesis of warburganal (1)........... 5

II. Meinwald's synthesis of muzigadial (2)........ 6

III. Synthetic approach to warburganal............. 10

IV. Synthetic approach to muzigadial.............. 11

V. Formation of 37 from 36........................ 24

VI. Formation of 41 and 42 from 37................ 28

VII. Formation of 92 from 91....................... 75

VIII. Intermediates in the conversion of 98 to 100.. 81

IX. Synthesis of warburganal...................... 91

X. Towards the synthesis of muzigadial........... 94

LIST OF ABBREVIATIONS

Bn	benzyl
cims	chemical ionization mass spectrum
m-CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	dimethylformamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
HMPA	hexamethylphosphoramide
hrms	high resolution mass spectrum
ir	infrared
LDA	lithium diisopropylamide
M	molar
MED	2-methyl-2-ethyl-1,3-dioxolane
MICA	bromomagnesium isopropyl cyclohexylamide
MoOPH	oxadiperoxymolybdenum(pyridine)-hexamethylphosphoramide
m.p.	melting point
MsCl	methanesulfonyl chloride
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
py	pyridine
r.t.	room temperature

S_N2	substitution nucleophilic bimolecular
TBDMS	_tert_-butyldimethylchlorosilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
_p_-TsOH	_p_-toluenesulfonic acid

INTRODUCTION

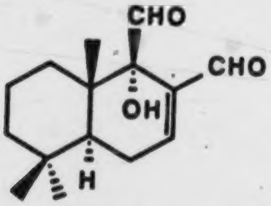
Man has been using chemicals for many years now to protect crops in the field and in storage from insects. Although the chemicals used are often effective in killing the target insect, most of the insecticides have other, often deleterious, effects on the ecological environment where they are dispersed. In the recent past considerable effort has been made to develop new methods to control pests in a more rational, less environmentally harmful way.

The study of the plant-insect interaction in its natural environment has enabled us to suggest alternative ways to control insect damage. It is thought that one of the functions of some of the secondary metabolites present in a plant is to protect against natural enemies. Compounds with insect antifeedant activity* isolated from plants include glycosides of steroidal alkaloids, aromatic steroids, quinones, germacrane sesquiterpenes, clerodanes, and iridoids.[1]

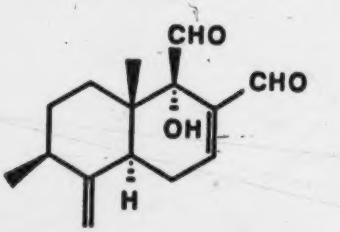
---

*Antifeedants are defined as substances which bring about a cessation of feeding, either temporarily or permanently, depending upon potency.

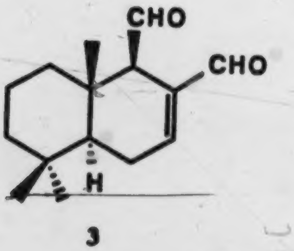
Kubo, Nakanashi and coworkers reported the isolation and identification of the drimane warburganal (**1**)[2] and muzigadial (**2**)[3] from the bark of the East African tree *Warburgia ugandensis* ("Muziga" in Swahili). The bark of *W. ugandensis* is employed widely in folk medicine and as a spice in food by the native people. These two drimane sesquiterpenes are among the strongest antifeedants against the African army worm, *Spodoptera exempta*. Leaves which had been dipped into 0.1 ppm solutions for 2 s are not eaten by the insects and lead to insect starvation.[2]



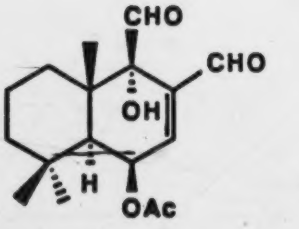
1



2



3



4

The enal-aldehyde moiety and its special arrangement play an essential role in the antifeedant activity, as indicated by simple correlations. Polygodial (**3**)[4] and cinnamodial (**4**)[5] are weaker antifeedants than warburganal

(**1**) and muzigadial (**2**). This suggests that the 9α-hydroxyl is essential for the strong activity and that the 6β-acetoxyl interferes in the binding of **4** decreasing its activity. When the 9 β-aldehyde group of polygodial (**3**) is inverted into the 9α orientation by mild treatment with base, antifeedant activity is lost[6]. It is interesting to note that active antifeedants taste hot and spicy to the human tongue, whereas all inactive derivatives are devoid of hot taste.[7]

Warburganal (**1**) displays an interesting biological profile. It is a potent antifungal (against Candida albicans, Trichophyton mentagrophytes) and antiyeast (against Saccharomyces postorianus) agent. In addition, warburganal (**1**) and muzigadial (**2**) show molluscicidal activity, an indication that they may be useful in the control of the dangerous schistosomes either by killing the schistosome-transmitting snail or by direct action.[6]

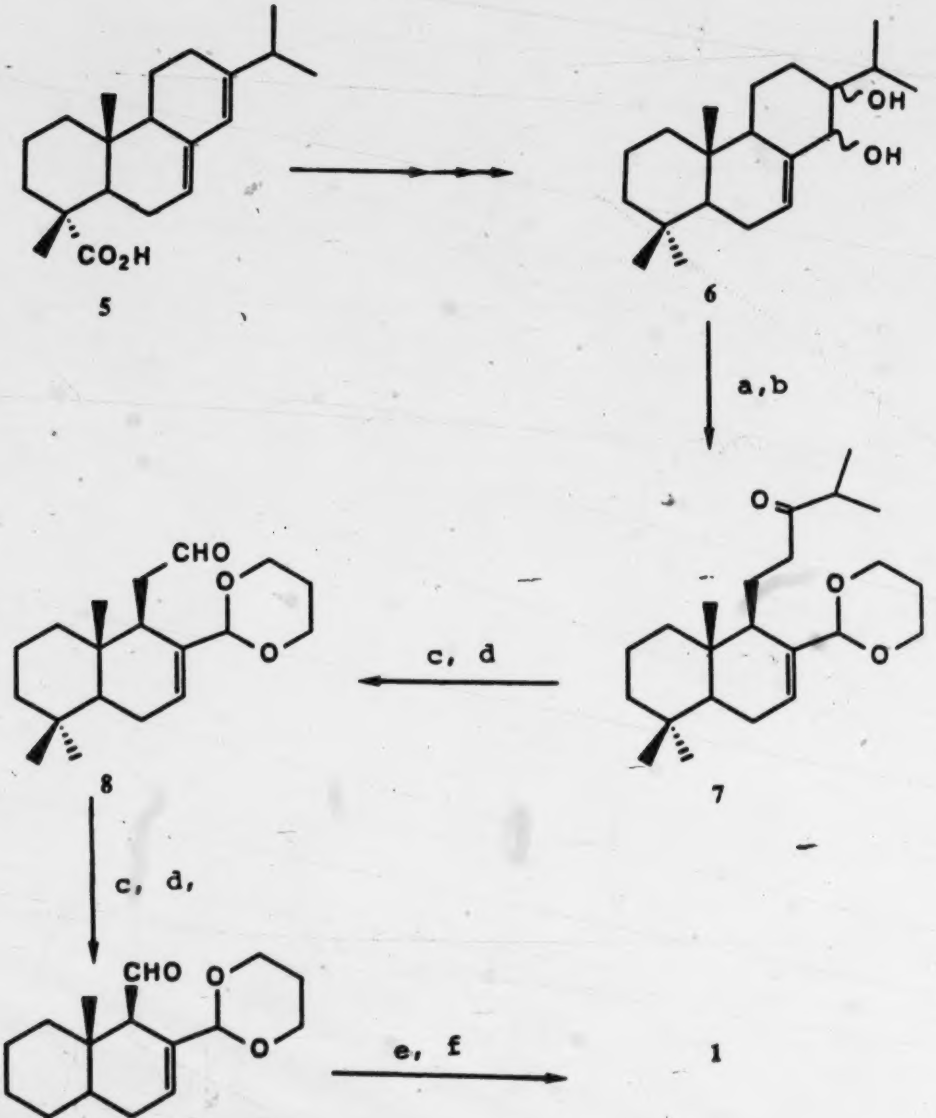
The remarkable biological properties of these substances coupled with their unique structure have attracted the attention of several groups. The total synthesis of warburganal (**1**) has been accomplished starting from (-)-abietic acid[8], 2,6,6-trimethyl-1-vinyl-cyclohex-1-ene,[9,10]isodrimenin,[11] 5,5,9-trimethyl-trans-1-decalone,[12] and through a metathesis/transannular ene sequence to the required trans-fused decalin derivative.[13] One synthesis has been reported for muzigadial (**2**) and it was accomplished starting from 9-methyl-$\Delta^{5(10)}$-octalin-1,6-dione.[1]

Ohno and coworkers[8] reported the synthesis of natural warburganal (**1**) using (-)-abietic acid (**5**) as chiral starting material (Scheme I). The double bond in ring B is in the correct position, thus they reduced the carboxylate to a methyl group, removed the extra five carbons, in ring C, and introduced the hydroxyl group at C-9. These transformations were carried out by regioselective hydroxylation of the double bond of ring C, esterification of the acid then reduction of the ester to methyl group by a well established sequence of reactions to obtain **6**. Oxidation of the diol with lead tetraacetate and protection of the resulting aldehyde afforded **7**. Ketone **7** was treated under kinetic conditions to form the enol silyl ether then subjected to ozonolysis to give **8**, and this was subjected to the same conditions to give the aldehyde **9**. Introduction of the tertiary hydroxyl group at C-9 was effected with Vedejs' reagent ($MoO_5 \cdot py \cdot HMPA$). This was followed by removal of the protecting group to afford (-)-warburganal (**1**).

Meinward and coworkers[1] used the commercially available ketone **10** as the starting material in their synthesis of muzigadial (**2**). Scheme II depicts the route

SCHEME I

Ohno's synthesis of warburganal (1)

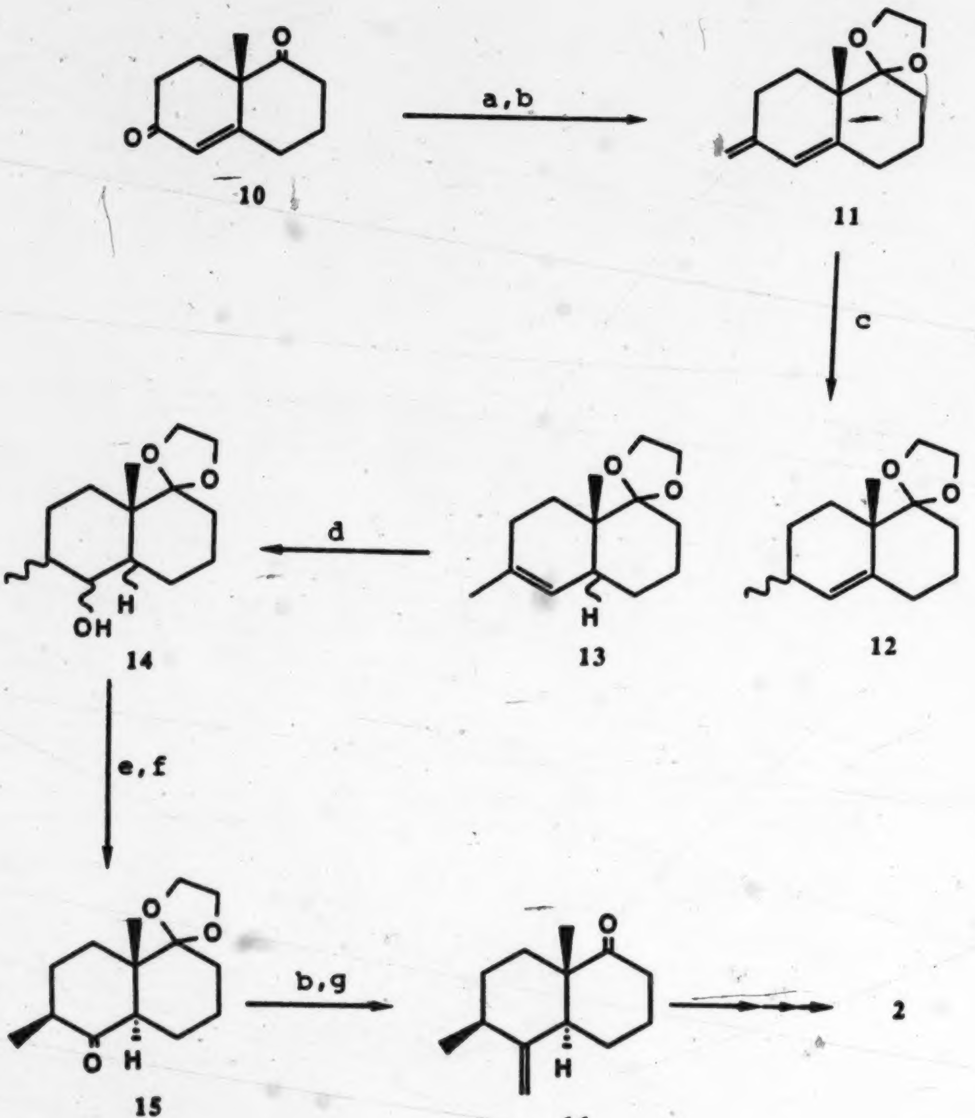


CO₂H
5
OH
OH
6
a,b
O
O
O
7
c, d
CHO
O
O
8
c, d,
CHO
O
O
9
e, f
1

a) $Pb(OAc)_4$; b) $HO(CH_2)_3OH$, TsOH; c) LDA, HMPA, TMSCl, Et_3N; d) O_3, Me_2S; e) LDA, $MoO_5 \cdot py \cdot HMPA$; f) TsOH/acetone

SCHEME II

Meinwald's synthesis of muzigadial (2)



a,b
c
d
e,f
b,g
10
11
12
13
14
15
16
2
OH
H
O

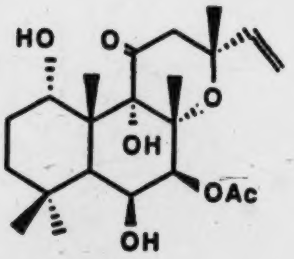
a) MED, $(CH_2OH)_2$; b) CH_2PPh_3; c) Li, NH_3; d) $BH_3 \cdot THF$, H_2O_2/NaOH; e) $CrO_3 \cdot py$; f) $NaOCH_3/CH_3OH$; g) 1N HCl/AcOH/THF

employed to introduce the secondary methyl and exocyclic methylene in ring A. Chemoselective protection of one carbonyl followed by a Wittig reaction afforded **11**. Reduction of the diene moiety with metallic lithium in ammonia yielded a mixture of isomeric olefins (**12** and **13**) which under oxidative hydroboration conditions provided the diasteriomeric alcohols **14**. Oxidation of the alcohols gave a mixture of decalones. Epimerization of the mixture under basic conditions afforded ketone **15**. Reaction of **15** with methylenetriphenylphosphorane provided the exocyclic olefin and was deprotected to give ketone **16**. This intermediate in their synthesis towards muzigadial (**2**) contained the required functionalities and stereochemistry in ring A. The intermediate **16** was elaborated in a further series of steps to provide racemic muzigadial (**2**).

Levopimaric acid (**17**) has been used in Ayer's laboratories as starting material in several attempts to synthesize natural products. It was, for example, used as starting material for the chemical correlation of atisine with the resin acids,[14] and in model studies on the atisane-acosane rearrangement.[15] Levopimaric acid (**17**) is a member of the so called resin acids. Resin acids are monocarboxylic acids having the typical molecular formula $C_{20}H_{30}O_2$ and are classed as being of the abietane and pimarane types. Resin acids are the major component of rosin, a solid resinous material that occurs naturally as part of the exudates (known as oleoresin) of pine and other coniferous trees.[16]

The availability and low cost of levopimaric acid (17) make it a very attractive starting material for the synthesis of natural products. An additional important feature is the fact that levopimaric acid is optically pure and thus may be transformed to optically active natural products.

We felt that warburganal (1) and muzigadial (2) could be synthesized by degradation and modification of levopimaric acid (17). We were also aware of the structural similarity of some of our proposed intermediates to forskolin, a cardioactive compound produced by the Indian medicinal plant Coleus forskohlii.[17]



FORSKOLIN

Levopimaric acid has the same absolute stereochemistry at C-5 and C-10 as warburganal, muzigadial, and forskolin. As well, the carboxyl functionality of levopimaric acid may be used to introduce the requisite functionality of ring A in muzigadial.

Our synthetic plan (Scheme III) required the transformation of the abietane skeleton to a drimane skeleton by removal of the top "isoprene unit". We envisaged that such a transformation could be achieved through formation of endoperoxide **18** since both oxygens of the endoperoxide could be used in the synthesis. The isoprene unit would be removed by cleavage of the olefin followed by cleavage of the bond between C-11 and C-12 utilizing the oxygen on C-12.* Functional group manipulation of the drimane intermediate **19** (dehydration of the C-8 alcohol, introduction of the C-9 hydroxyl group, and the reduction of the methyl ester to a methyl group) would furnish 4α-methoxycarbonylwarburganal.** (**20**) and warburganal (**1**).

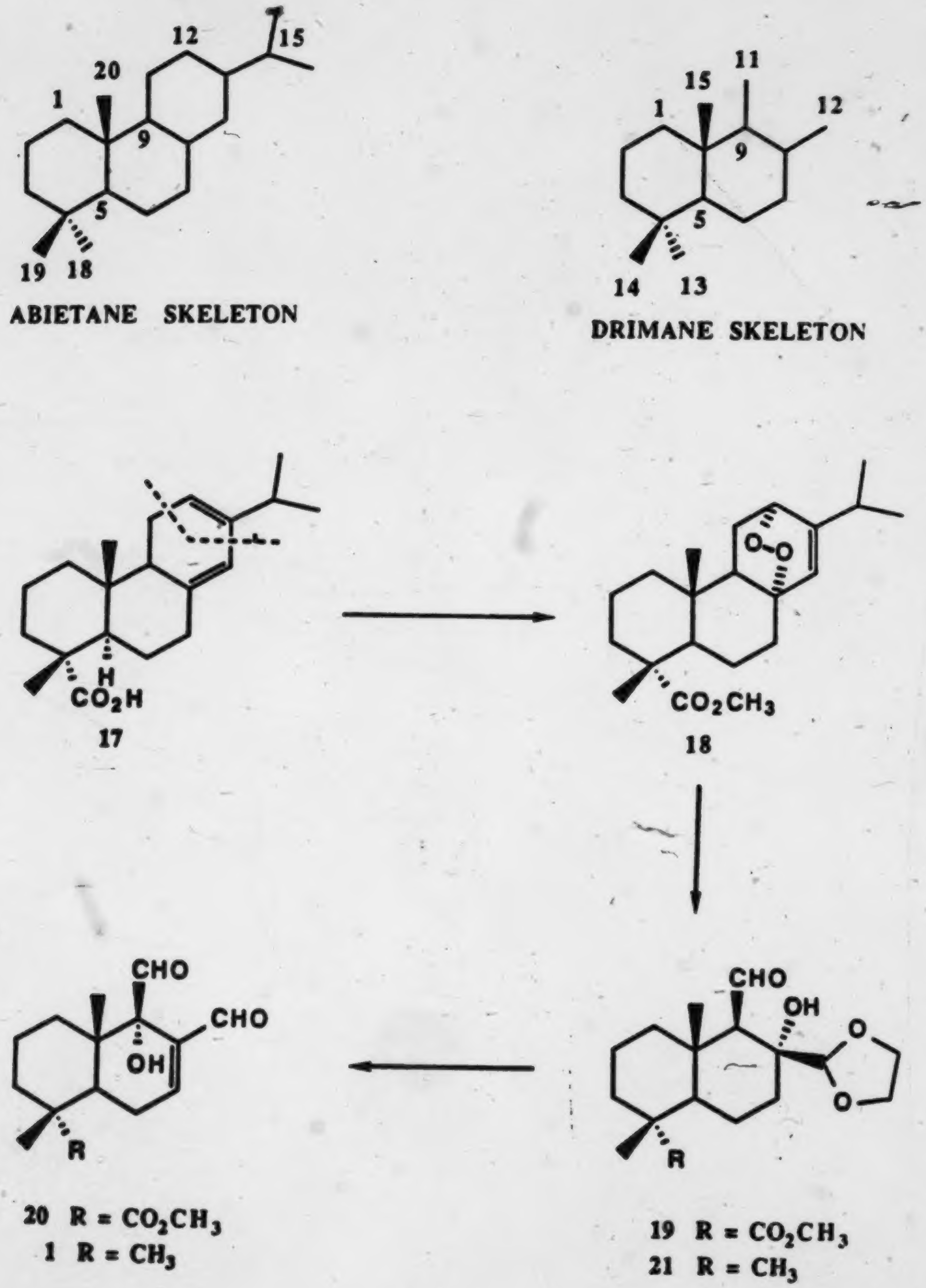
---

*All synthetic intermediates are numbered according to the abietane skeleton conventional numbering system except for those intermediates possessing the drimane skeleton. These are numbered according to the conventional drimane numbering system.

**It is recognized that this name is not strictly correct, the compound is the 4α-methoxycarbonyl congener.

SCHEME III

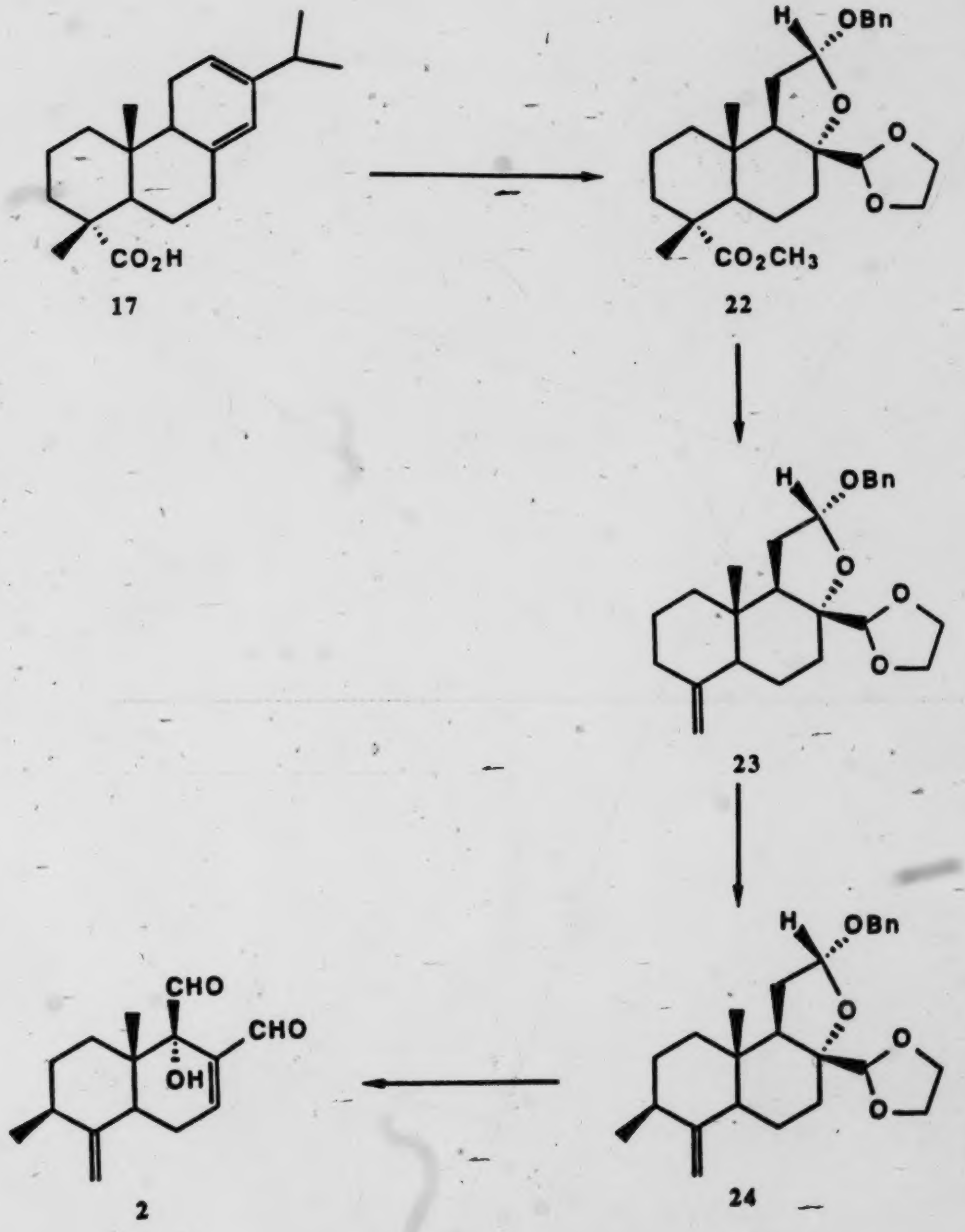
Synthetic approach to warburganal



12
15
20
1
9
5
19 18
ABIETANE SKELETON
11
15
12
1
9
5
14 13
DRIMANE SKELETON
H
CO_2H
17
O-O
CO_2CH_3
18
CHO
OH
O
O
R
19 R = CO_2CH_3
21 R = CH_3
CHO
CHO
OH
R
20 R = CO_2CH_3
1 R = CH_3

SCHEME IV

Synthetic approach to muzigadial


CO₂H
17
H
OBn
O
O
O
CO₂CH₃
22
H
OBn
O
O
O
23
H
OBn
O
O
O
24
CHO
CHO
OH
2

The synthesis of muzigadial (**2**) (Scheme IV) would require many of the transformations used in the synthesis of warburganal (**1**). An intermediate prepared in the synthesis of 1 would be used to carry out transformations on ring A to give the muzigadial ring A functionality. We envisaged that formation of the exocyclic olefin **23** would be the first step. The double bond of **23** could be used to activate C-3 to introduce the C-3 methyl group (**24**). Formation of intermediate **24** should allow synthesis of muzigadial (**2**) to be completed using a functional group transformation sequence similar to that employed for warburganal (**1**).

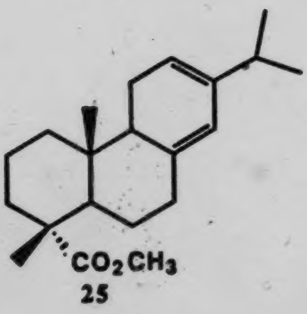
To facilitate the discussion of the synthetic studies, the results will be presented under the following four headings. (1) Transformation of the abietane skeleton to the drimane skeleton. (2) Synthesis of 4α-methoxycarbonylwarburganal (**20**). (3) Reduction of the carboxyl group to a methyl group: synthesis of warburganal (**1**). (4) Ring A transformations: Towards the synthesis of muzigadial (**2**).

RESULTS AND DISCUSSION

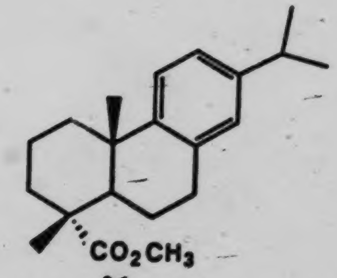
1. Transformation of the Abietane Skeleton to the Drimane Skeleton

Levopimaric acid (**17**) was isolated from the pine oleoresin using the procedure reported by Hedrick (reported[18] $[\alpha]_D$ - 265°, found $[\alpha]_D$ - 265°). Esterification of **17** with diazomethane afforded methyl levopimarate (**25**) in 98% yield. The ^{1}H nmr spectrum of **25**, displays two vinyl protons (δ5.50 (d, 1.5 Hz) and δ5.11 (t, 4 Hz)), two quaternary methyl groups (δ1.17 and δ0.89), an isopropyl group (δ0.95, d, 7 Hz, 6H), and a carbomethoxy group (δ3.65).

Endoperoxide **18** was formed by photooxygenation of **25** as described by Lawrence[19] using rose bengal as sensitizer. An ethanolic solution of **25** was irradiated with a 40 watt incandescent lamp at room temperature for 9 h during which time oxygen was bubbled through the solution. Endoperoxide **18** was formed as the major



25

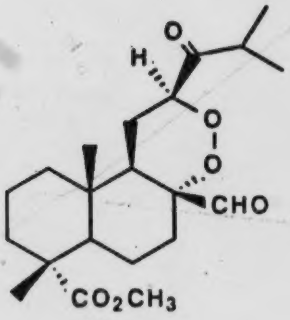


26

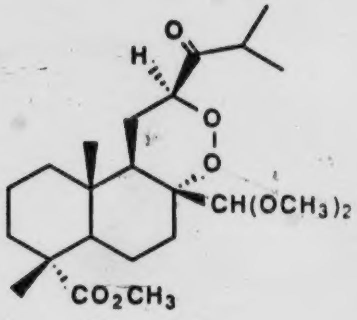
product along with a small amount of methyl dehydroabietate (**26**). Addition of singlet oxygen to the diene of **25** occurs from the less hindered α face. The high resolution mass spectrum (hrms) of **18** shows a molecular ion at m/z 348 corresponding to the molecular formula $C_{21}H_{32}O_4$ and a fragment ion at m/z 316 ($C_{21}H_{32}O_2$) for M^+ minus two oxygens. The ^1H nmr spectrum of **18** displays a vinyl proton, an isopropyl group, a quaternary methyl group (δ1.14), and a high field angular methyl group (δ0.57). The shift of this signal to high field is caused by the shielding effect of the double bond.[20]

Intermediate **18** is suitably oxygenated at C-12 for the removal of the "isoprene unit". We planned to carry out this transformation by cleavage of the C-13, C-14 double bonds followed by selective protection of the resultant aldehyde. Treatment of endoperoxide **18** with ozone at -78°C in CH_2Cl_2/CH_3OH (9:1), followed by reductive work-up with methyl sulfide[21] gave compound **27** as an oil. Its ^1H nmr spectrum is consistent with the assigned structure, in particular, it displays an aldehyde proton as a singlet at δ9.77. A small peak in the hrms of **27** at m/z 380 ($C_{21}H_{32}O_6$) confirms its molecular formula.

Protection of the aldehyde as the dimethyl acetal was achieved by treatment of **27** with methyl orthoformate under



27

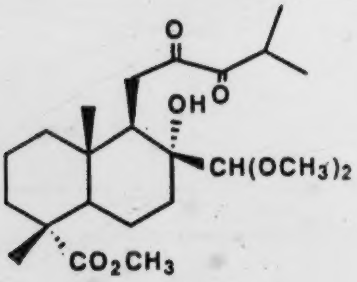


28

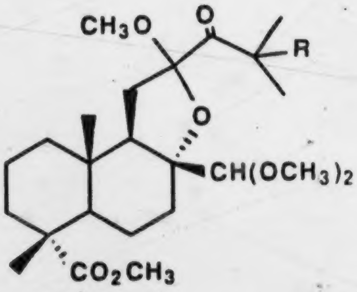
mild conditions (p-toluenesulfonic acid, p-TsOH, room temperature) to afford **28** in 68% overall yield from endoperoxide **18**. Chemical ionization mass spectrum (cims) of compound **28** shows an ion at m/z 444 ($M^+ + 18$). The ^1H nmr spectrum of **28** displays three methoxyl groups as singlets (δ3.67, δ3.60, δ3.46) and a one proton quintet at δ2.96 (7 Hz). The other signals are consistent with the proposed structure for intermediate **28**.

We felt that cleavage of the peroxide bridge of **28** to give an α-diketone would provide an useful intermediate. Methods of conversion of endoperoxides to β or γ hydroxyketones have been reported.[22] The transformation is carried out by abstraction of the proton geminal to the peroxide, inducing the heterolytic cleavage of the O-O bond. Mild bases such as amines or alkoxides are used if the geminal proton is activated by another functionality.

Compound **28** was treated with triethylamine (Et_3N) in chloroform for 48 h. The α-diketone **29** was obtained as a yellow oil after purification of the crude product. A yellow color is characteristic of α-diketones.[23] The infrared spectrum (ir) of **29** shows absorption bands characteristic of hydroxyl (3456 cm^{-1}) and carbonyl (1725 cm^{-1}) groups. The ^1H nmr spectrum of **29** shows that almost all of its signals are repeated, indicating that **29** exists in solution as a tautomeric mixture of the 5-membered hemiacetal, 6-membered hemiacetal, and the hydroxy diketone form.



29



30 R = H
31 R = D

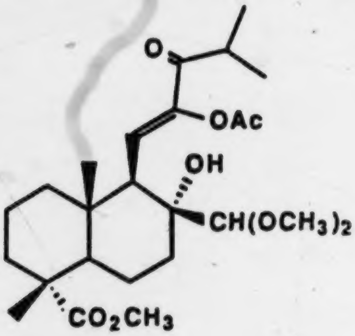
With the α-diketone **29** in hand, we sought methods of preparation of the enol derivative of the C-12 carbonyl. To avoid problems in distinguishing between the C-12 and C-13 carbonyls, we attempted to protect the C-13 carbonyl as its corresponding 6-membered methyl acetal.

Treatment of α-diketone **29** under standard conditions for acetal formation (p-TsOH/CH(OCH$_3$)$_3$) gave a product (**30**) which provided colorless needles (m.p. 180-182°C) after recrystallization. Analysis of the spectroscopic data for this crystalline compound suggested that the 5-membered acetal had formed instead of the desired 6-membered acetal. The ^{1}H nmr spectrum of compound **30** displays four singlet methoxyl groups (δ3.70, δ3.56, δ3.26, δ3.25) and a quintet at δ3.34 (7 Hz) corresponding to the methine of the isopropyl group. The chemical shift observed for the methine proton was more appropriate for a proton alpha to a ketone rather than to an acetal.

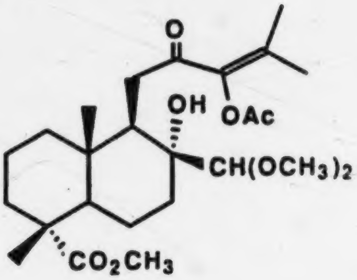
The structure of compound **30** was confirmed by the following experiment. Treatment of **30** with sodium methoxide in methanol-d$_1$ yielded compound **31**. Its ir spectrum shows an absorption band for carbon deuterium stretching (2190 cm^{-1}). The ^{1}H nmr spectrum of **31** does not show the isopropyl methine (δ3.34, quintet) but shows the methyl groups of the isopropyl moiety as two singlets (δ1.12 and δ1.08). These data confirm the proposed structure for methyl acetal **30**.

We found that protection of the C-13 carbonyl of **29** was not required for formation of the desired α-oxo-enol acetate. When α-diketone **29** was treated with diisopropylethylamine (i-Pr$_2$NEt) and acetic anhydride

(Ac_2O) two products were formed in a ratio of 13:1. The use of triethylamine as the base gave a product ratio of 1:1. Examination of the spectral data of the product revealed that the desired enol acetate **32** was present as the major component in the diisopropylethylamine catalyzed reaction.



32



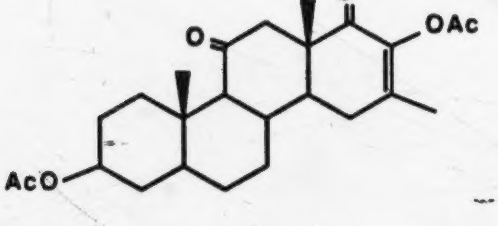
33

The ir spectrum of **32** shows absorption bands for hydroxyl (3550 cm^{-1}), ester (1759 cm^{-1} and 1725 cm^{-1}), conjugated carbonyl (1686 cm^{-1}), olefin (1640 cm^{-1}), and the characteristic strong band for C-O stretching of an enol acetate (1212 cm^{-1}).[24] The cims of keto enol acetate **32** has a peak at m/z 486 ($M^+ + 18$). Its ^1H nmr spectrum displays a vinyl proton as a doublet at δ6.45 (11 Hz), the isopropyl methine as a quintet at δ3.06 (7 Hz) and an acetoxyl methyl singlet at δ2.22. The stereochemistry of the double bond was assigned as (Z) because of the low field chemical shift of the vinyl proton.[25]

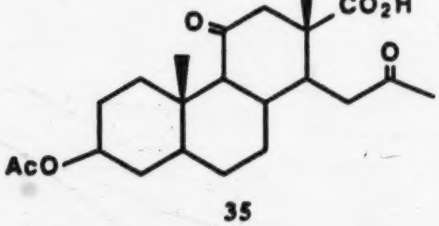
The minor component, keto enol acetate **33** shows ir and cims spectra similar to those of **32**. However the ^{1}H nmr spectrum of **33** does not display the characteristic signal for the isopropyl methine indicating that enol acetate formation has occurred between C-13 and C-15.

With enol acetate **32** in hand, we planned to remove the "isoprene unit" by oxidative cleavage of the double bond. When compound **32** was treated with ozone at different temperatures (-70°C to r.t.) over a long period of time (3 h) only starting material was recovered. Treatment of **32** with osmium tetroxide under the Lemieux-Johnson conditions[26] or in pyridine[27] yielded only recovered starting material.

Potassium permanganate has been used for the oxidation of the diosphenol acetate **34** to the ketoacid **35**.[28] When compound **32** was treated with potassium permanganate under the same reaction conditions the only material recovered after work-up was the unreacted enol acetate **32**.



34



35

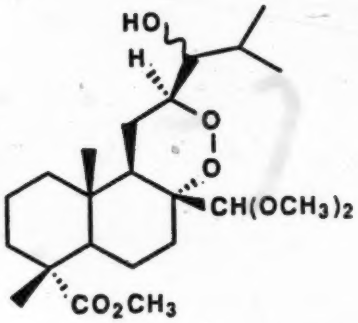
Reaction of **32** with ruthenium tetraoxide,[29] or m-chloroperbenzoic acid for prolonged reaction times led to recovery of unreacted compound **32**.

The inertness of enol acetate **32** to a wide variety of oxidizing reagents was unexpected. This lack of reactivity of **32** may be explained by the following factors: It may be difficult for bulky oxidizing agents to approach the congested environment of the olefin, and/or the olefin may be deactivated by conjugation with the carbonyl.

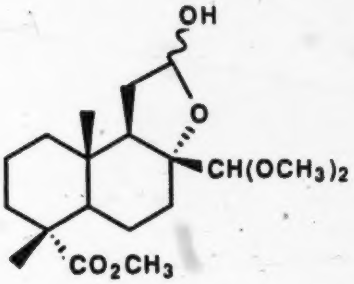
We thought that reduction of the conjugated ketone of **32** to the corresponding allylic alcohol might make the enol acetate more reactive to oxidative cleavage reagents. However, attempted reduction of compund **32** under the Luche's conditions[30] ($NaBH_4/CeCl_3$ in methanol, ethanol, or iso-propyl alcohol) gave a complex mixture of products.

Thwarted in our attempts to cleave the enol acetate **32**, we turned our attention to a different approach to remove the "isoprene unit".

Reduction of the ketone **28** with $NaBH_4$ under standard conditions gave an epimeric mixture of alcohols **36**. The ir spectrum of **36** displays an absorption band for an hydroxyl group at 3537 cm^{-1}. The ^1H nmr spectrum of **36** is consistent with the assigned structure, in particular, it shows the protons geminal to the hydroxyl group at δ3.35 (dd, 11.5, 3 Hz) and δ3.12 (dd, 8.5, 4.5 Hz) in a ratio of 3:2 respectively, indicating the epimeric nature of alcohol **36**.



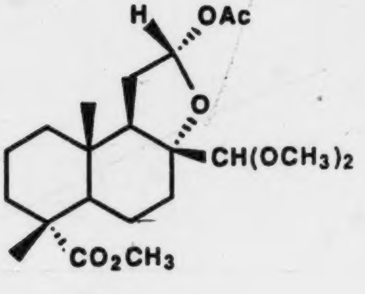
36



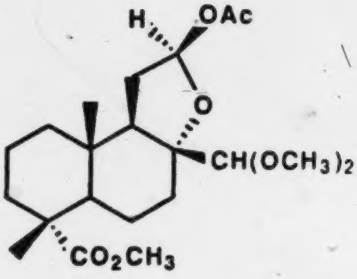
37

We found that the epimeric mixture of alcohols is converted to the hemiacetal **37** when it is treated with base (CH_3ONa/CH_3OH) at room temperature. The structure of compound **37** was confirmed as follows. Its cims shows a M^+ + 18 ion at m/z 374 (17%) and a molecular ion at m/z 356 (18%) for $C_{19}H_{32}O_6$. The hrms of **37** shows a fragment at m/z 338 ($C_{19}H_{30}O_5$) corresponding to the molecular ion minus water. The molecular formula of **37** has C_4H_8O less than **36** ($C_{23}H_{40}O_7$). The ir spectrum of **37** shows an absorption band at 3480 cm^{-1} for an hydroxyl group and at 1725 cm^{-1} for the ester group. The ^1H nmr spectrum indicates that **37** exists as a mixture of epimers. It displays signals for two quaternary methyl and three methoxyl groups. The characteristic signals for the isopropyl group were absent in the spectrum.

Acetylation of 37 under standard conditions (Ac_2O/Et_3N) gave an epimeric mixture of acetal acetates 38 and 39 which were separated and characterized. The ir and hrms spectra are in agreement with the assigned structures of 38 and 39. The α- and β-epimers of the acetal acetate were identified by analysis of the ^1H nmr spectrum of 38 and 39.



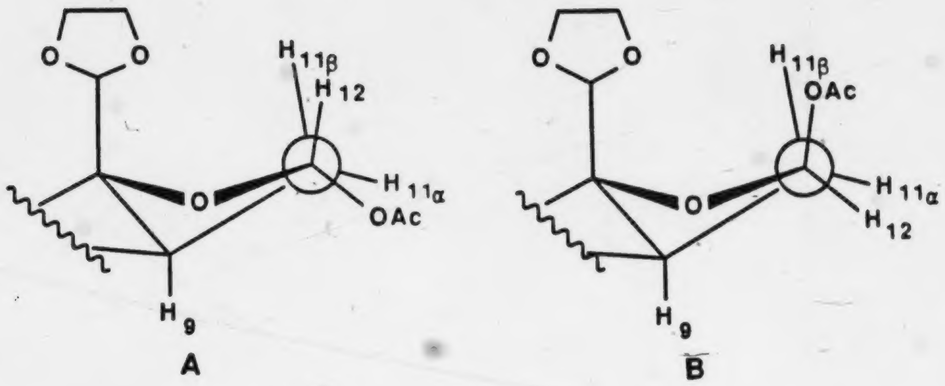
38



39

The ^1H nmr spectrum of 38 displays H-12 as a one proton doublet at δ6.37 (5.5 Hz) coupled to one proton at δ2.46 (ddd, 14, 11.5, 5.5 Hz). Irradiation of the signal at δ2.46 collapses the signals at δ1.95 (dd, 14, 7 Hz, H-11α) and δ1.54 (dd, 11.5, 7 Hz, H-9) to doublets. Examination of molecular models reveals that H-12 possesses a dihedral angle of ca. 90° with H-11α when the acetoxyl group has an α orientation (Figure 1 A). The

Figure 1. Partial Newman projection of **38** and **39**.



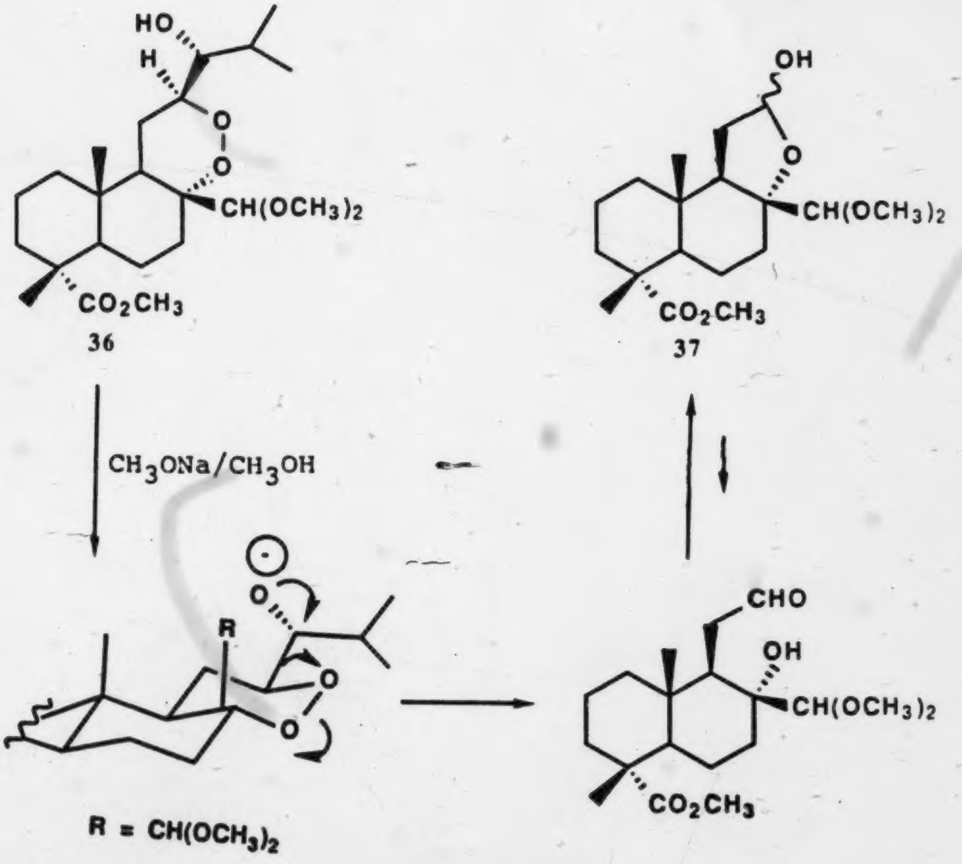
Karplus rule^{31} would predict a coupling constant of *ca.* 0 Hz between H-12 and H-11α which is observed in the ^{1}H nmr spectrum of **38**.

The ^{1}H nmr spectrum of **39** displays H-12 as a one proton triplet at δ6.16 (5.5 Hz). Molecular models of **39** are in agreement with the multiplicity observed for H-12 in its ^{1}H nmr (Figure 1 B). Further support for this stereochemical assignment is obtained from subsequent intermediates in the synthesis.

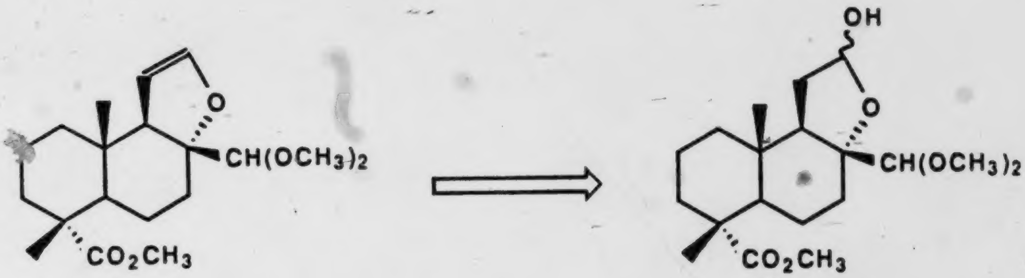
The transformation of **36** to **37** can be classified as an heterolytic fragmentation.^{32} A plausible mechanism for the formation of **37** from **36** is shown in Scheme V. Such a synchronous mechanism operates only when the orbital of the free pair of electrons of the alkoxide and the O-O bond are anti and parallel antiperiplanar to the C-C bond to be broken.

SCHEME V

Formation of **37** from **36**


HO
H
O
O
CH(OCH3)2
CO2CH3
36
OH
O
CH(OCH3)2
CO2CH3
37
CH3ONa/CH3OH
O
R
O
O
R = CH(OCH3)2
CHO
OH
CH(OCH3)2
CO2CH3

The carbon skeleton of **37** closely resembles that of the drimane sesquiterpenes except for an extra carbon at C-11. We felt that this carbon could be removed by oxidation of enol ether **40**, which in turn could be formed by dehydration of **37**.



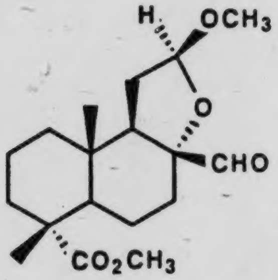
40 37

It is expected that enol ether **40** would be more reactive towards oxidizing reagents than compound **32** for two reasons: The olefin should be more accessible to attack by the oxidant and the enol ether is expected to be more reactive (toward electrophile) than the ketoenol acetate.

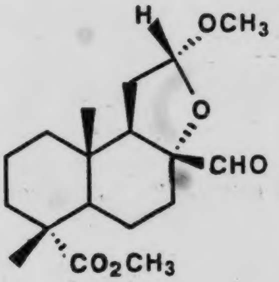
van Tamelen and coworkers[33] have reported the formation of the Δ^2-dihydrofuran from γ-hydroxyaldehydes by pyrolysis (285-295°C, 0.01 mm Hg) of the corresponding acetal acetate. With other dehydrating reagents Δ^2-dihydrofurans were not obtained.

We attempted to dehydrate hemiacetal **37** by a variety of mild dehydration methods. Treatment of **37** with phosphorous oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), p-toluenesulfonyl isocyanate, or Burgess' reagent[34] gave a complex mixture of products.

However, when **37** was treated with mesyl chloride (Et_3N/CH_2Cl_2)[35] two cyclic methyl acetals were obtained (**41** and **42**). Similar results were obtained by treatment of **37** with iodine (refluxing toluene) or p-TsOH (r.t.).



41



42

The cims of compound **41** has a peak at m/z 342 for $M^+ + 18$ and its hrms shows a fragment at m/z 295 (100%) corresponding to $C_{17}H_{27}O_4$ (M^+ - CHO). The ^{13}C nmr spectrum shows signals for eighteen carbons confirming the molecular formula obtained from the mass spectra.

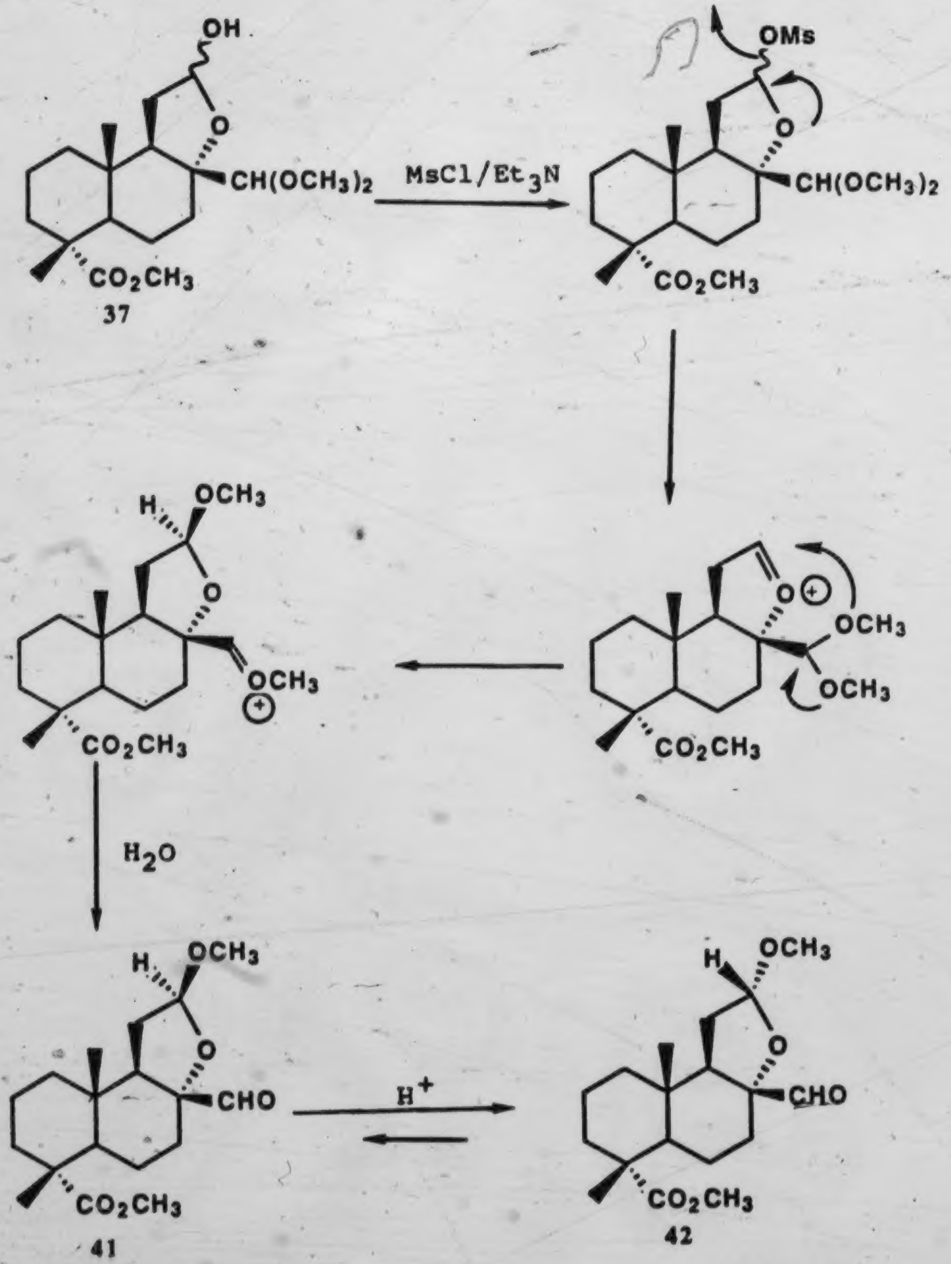
The ^1H nmr spectrum of **41** displays two singlets for quaternary methyl groups (δ1.10 and δ0.82), two singlets for methoxyl group (δ3.64 and δ3.39), a doublet at δ9.82 (1.5 Hz) for an aldehydic proton, and a triplet at δ5.24 (5 Hz) for H-12. H-7β appears as a doublet of triplets at δ2.44 (12, 3 Hz). Its unusual downfield chemical shift is caused by the anisotropy of the oxygen on C-8.[36] Decoupling experiments show that the aldehydic proton and the H-7β are coupled to the same proton in the complex region at δ1.3-1.15. Nuclear Overhauser enhancement (nOe) experiments supported the proposed structure for **41**. Presaturation of the signal at δ9.82 gives an enhancement of 7% at δ1.10 and 17% to the angular methyl (δ0.82).

The spectroscopic data for the aldehyde **42** (ir, hrms, and ^{13}C nmr) is very similar to that for compound **41**. The ^{1}H nmr spectrum of **42** is consistent with the proposed structure, in particular, it displays a doublet at δ5.31 (5.5 Hz) for H-12 and a singlet at δ9.61 for an aldehydic proton. A nOe experiment gave the following results: Presaturation of the angular methyl group (δ0.76) induces an enhancement of 12% for the singlet at δ9.61, 7.5% for the signal at δ2.06 (H-11β), and 15% for the signal at δ1.13 (C-4 CH_3). The methoxyl group on C-12 was assigned the α orientation due to the multiplicity of the signal at δ5.31 (d, 5.5 Hz).

The formation of **41** and **42** may be rationalized as shown in Scheme VI. Two observations support our proposed mechanism: The addition of water to the reaction mixture after **37** had been consumed increases the rate of the formation of **41** (as observed by thin layer chromatography,

SCHEME VI

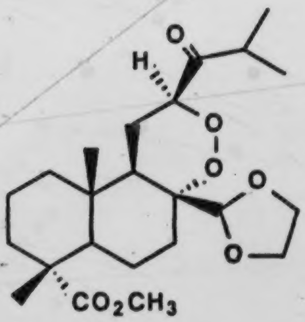
Formation of 41 and 42 from 37


OH
CH(OCH3)2
CO2CH3
37
MsCl/Et3N
OMs
CH(OCH3)2
CO2CH3
OCH3
OCH3
CO2CH3
H
OCH3
OCH3
CO2CH3
H2O
H
OCH3
CHO
CO2CH3
41
H+
H
OCH3
CHO
CO2CH3
42

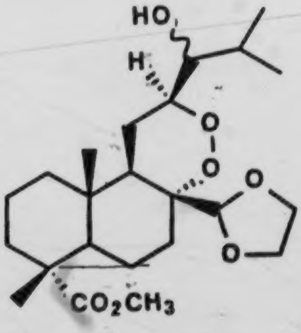
tlc), and long reaction times increase the amount of the more stable cyclic methyl acetal **42**.

At this point we decided to change the aldehyde protecting group to the more stable dioxolane because it would not migrate during the mesylation reaction.

Ketoaldehyde **27** was protected under mild conditions[37] (ethylene glycol/$CH(OCH_3)_3$/benzene, p-TsOH, 45°, 160 mm Hg) to obtain **43**. The overall yield of **43** from levopimaric acid (**17**) is 49% when the reaction sequence is carried out without purification until the final step. The ^1H nmr spectrum of **43** displays signals consistent with the assigned structure and shows a singlet at $\delta5.37$ and a four proton complex multiplet at $\delta4.20\text{-}3.84$ as is characteristic of protons of a dioxolane.



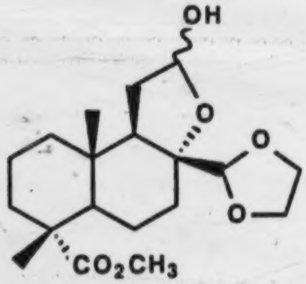
43



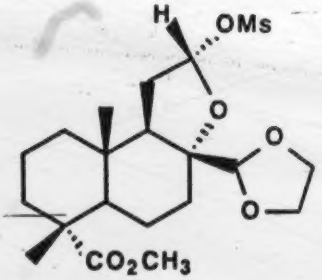
44

Reduction of the ketone **43** ($NaBH_4/CH_2Cl_2/MeOH$) yielded a mixture of epimeric alcohols **44** in a ratio 7:3 as determined by ^1H nmr (from the signals of the protons geminal to the hydroxyl, δ3.30 (dd, 8, 3 Hz) and δ3.18 (t, 5.5 Hz)).

Heterolytic fragmentation of **44** under basic conditions (CH_3ONa/CH_3OH) afforded hemiacetal **45**. The ir spectrum of **45** shows a characteristic absorption band for an hydroxyl group (3428 cm^{-1}) in addition to the ester carbonyl band (1726 cm^{-1}). Its hrms shows the molecular ion at m/z 354 ($C_{19}H_{30}O_6$).



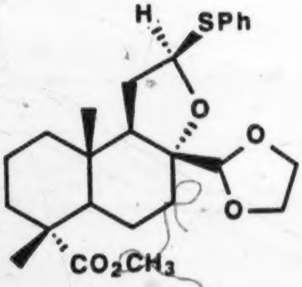
45



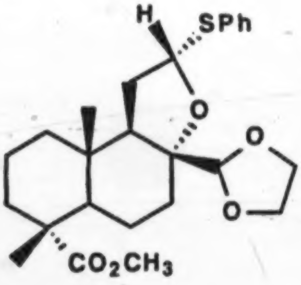
46

With the stable ethylene acetal protecting group on compound **45**, mesylate **46** was formed under standard conditions ($MsCl/Et_3N/CH_2Cl_2$). The ir spectrum of **46** shows the characteristic bands for sulfonates[38] (1358, 1335, 1100 cm^{-1}). Its ^1H nmr spectrum displays the methyl group of the sulfonate as a singlet at δ3.37. The orientation of the mesyl group was assigned α because of the multiplicity observed for the H-12 signal (δ5.06, d, 5.75 Hz). Attempts to transform **46** to the enol ether failed (1,8-diazabicyclo[5.4.0]undec-7-ene(DBU)/refluxing toluene).[39]

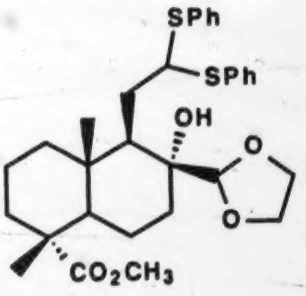
Pyrolysis of sulfoxides has been used to prepare olefins in a wide variety of molecules.[40] We felt that this method might be useful in the formation of the desired enol ether. The required sulfur analog of **45** could be formed by an acetal exchange reaction. Hemiacetal **45** was mixed with thiophenol (cat. amount of trifluoroacetic acid (TFA)/CH_2Cl_2). Work-up of the reaction mixture yielded three products. The two major components, **47** and **48**, are epimeric hemithioacetals. The ir spectra of **47** and **48** are very similar with characteristic bands for monosubstituted benzene ring (740 and 690 cm^{-1}). The hrms of **47** and **48** each show a fragment corresponding to the molecular ion at m/z 446 ($C_{25}H_{34}O_5S$).



47



48

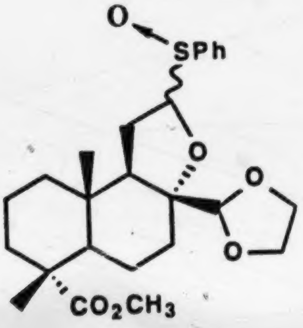


49

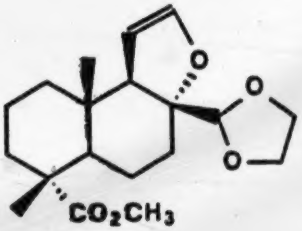
The epimeric hemithioacetals **47** and **48** are distinguished by their ^1H nmr spectra. The minor component **47** displays H-12 as a doublet of doublets at δ5.54 (9, 6.5 Hz) and shows one dioxolane proton as a complex multiplet at δ4.39. Irradiation of the signal at δ4.39 collapses the multiplet at δ4.10-3.71 indicating that it is one of the protons of the dioxolane group. The coupling constants of H-12 and the deshielded nature of one of the protons of the dioxolane indicate the thiophenol group has the β orientation. The major component **48** was assigned as the α epimer (δ5.63, dd, 8, 1.5 Hz, H-12).

The third component of the mixture was identified as the thioacetal **49** on the basis of the following spectral evidence. The ir spectrum of **49** shows hydroxyl absorption (3512 cm^{-1}) while its ^1H nmr spectrum shows an hydroxyl signal (δ2.51, s, D_2O exchangeable) and ten aromatic protons between δ7.59-7.19. Compound **49** can be converted to **47** and **48** under acidic conditions (TFA/CH_2Cl_2). The overall yield of the hemithioacetals from the ketoperoxide **43** is 75% when the reaction sequence is carried out with no purification until the last step.

The hemithioacetals **47** and **48** were oxidized with one eq. of m-chloroperbenzoic acid (m-CPBA) to the corresponding sulfoxides. The ir spectrum of compound **50** shows the characteristic bands for sulfoxides.[38] Pyrolysis of the sulfoxides **50** in the presence of triethylphosphite (added to destroy the sulfenic acid formed in the reaction[41]) (5 eq., refluxing xylenes) afforded the strained enol ether **51**.



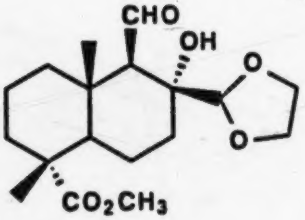
50



51

The acid sensitive enol ether **51** was identified by its spectral properties. The ir spectrum of **51** has a band at 1585 cm^{-1} characteristic of Δ^2-dihydrofurans.[33] Its ^1H nmr spectrum was consistent with the assigned structure, in particular, it displays signals at δ6.40 (t, 3.25, H-12) and δ5.17 (br s, H-11). Conversion of the hemiacetal **37** to enol ether **51** by means of the hemithioacetals proved to be an excellent method of preparation. The overall yield of **51** from **47** and **48** was 64%.

Cleavage of the double bond of enol ether **51** was carried out with ozone (CH_2Cl_2/MeOH), followed by reductive work-up ($((CH_3)_2S)$). The only product isolated after work-up was identified as the β-hydroxyaldehyde **19**. The hrms has a peak at m/z 340 corresponding to the molecular formula $C_{18}H_{28}O_6$. The ^1H nmr spectrum of **19** displays a one proton doublet at δ9.92 (3 Hz) for the aldehyde and another one proton doublet at δ2.17 (3 Hz) for H-9. The hydroxyl group was detected in the ir spectrum (3505 cm^{-1}) and ^1H nmr spectrum (δ2.97, s).



19

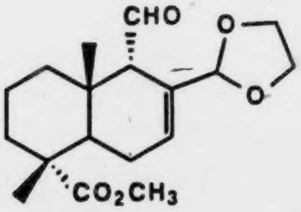
At this point in the synthesis we have transformed levopimaric acid (**17**), with an abietane skeleton, to aldehyde **19** with the desired drimane skeleton.

2. Synthesis of 4α-Methoxycarbonylwarburganal (**20**)

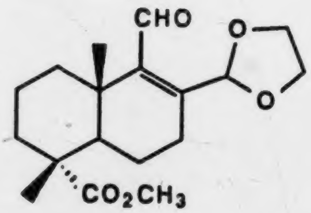
The next sequence of reactions in our synthetic plan was the modification of the functional groups in the drimane skeleton to that of warburganal (**1**). The aldehyde **19** has the required oxidation level at C-11 and C-12. The double bond could be introduced by elimination of the hydroxyl on C-8. The α-hydroxyaldehyde moiety could be derived by stereoselective oxidation of the corresponding enolate.

Attempts to dehydrate the hydroxyaldehyde **19** with $POCl_3$, $SOCl_2$, or *p*-toluenesulfonyl isocyanate yielded only complex mixtures. Similar complex mixtures were obtained when iodine, *p*-TsOH, or camphorsulfonic acid (CSA) was used as the dehydrating reagent. Treatment of **19** with mesyl chloride (Et_3N/CH_2Cl_2) or Ac_2O (4-dimethylaminopyridine (DMAP)/py) under standard conditions afforded only the starting material.

Dehydration of the hydroxyaldehyde **19** was achieved, however, under basic conditions (1 *M* $NaOH/CH_3OH$, reflux) to yield the β,γ-unsaturated aldehyde **52**. The hrms of **52** shows a peak at m/z 322 corresponding to the molecular formula $C_{18}H_{26}O_5$, and its ir spectrum shows characteristic absorption bands for ester (1720 cm^{-1}), aldehyde (1708 cm^{-1}), and olefin (1675 cm^{-1}). The ^1H nmr spectrum of compound **52** displays signals for two quaternary methyl groups (δ1.26 and δ0.99), a methoxyl group (δ3.68), the ethylene portion of the dioxolane (δ4.09-3.73 4H), a vinyl proton as a triplet (δ6.19, 3.5 Hz), and an aldehydic proton as a doublet (δ9.64, 5 Hz). The multiplicity of the aldehyde signal at δ9.64 in the ^1H nmr and the observation of one vinyl proton is consistent with structure **52**.



52

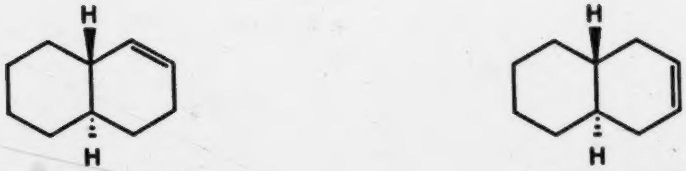


53

Presumably, the β,γ-unsaturated aldehyde **52** arises by isomerization of the initially formed α,β-unsaturated aldehyde **53**, the driving force for the isomerization being the greater stability of the C-7, C-8 double bond over that of the C-8, C-9 double bond. It is known that Δ^2-trans-octalin is more stable than its Δ^1 isomer (Figure 2).[43] Similar observations have been made in steroid chemistry.[44]

The α orientation of the aldehyde group on **52** was confirmed after removal of the protecting group. Treatment of **52** with *p*-TsOH in acetone yielded the dialdehyde **54**. The ^1H nmr spectrum of **54** displays aldehydic protons at δ9.85 (d, 2.5 Hz) and δ9.41 (s).

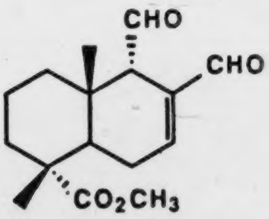
Figure 2. 1- and 2-trans-octalin



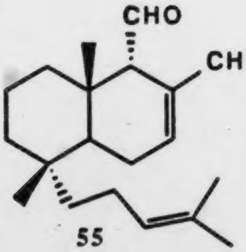
1-trans-octalin

2-trans-octalin

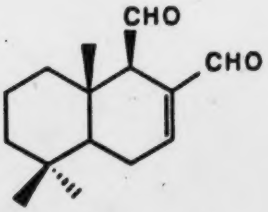
The chemical shift of the aldehydic protons in the ^1H nmr reported for isosacculatal (**55**)[44] and polygodial (**3**)[10] is δ9.83 (d, 2.5 Hz), δ9.38 (s) and δ9.54 (d, 5 Hz), δ9.47 (s), respectively. The similarity of the ^1H nmr spectrum of **54** with that reported for **55** suggest that the C-9 CHO in **54** has the α-orientation. Thus compound **52** may be assigned the same relative stereochemistry at C-9.



54



55

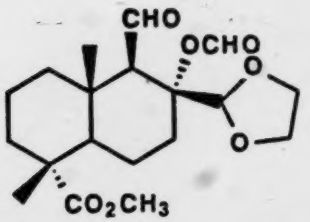


3

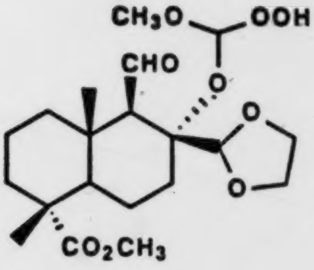
The tendency of the aldehyde of **52** to adopt a quasi-axial orientation may be to avoid the allylic interaction ($A^{1,2}$) with the dioxolane.[45] Similar observations have been reported for polygodial (**3**). Treatment of **3** under mildly basic conditions afforded a mixture of products, the major component being the C-9 α epimer.[46]

Because of the low yield (~40%) obtained in the dehydration of compound **3**, we investigated a different method of accomplishing the same transformation. Ozonolysis of olefins followed by reductive work-up (e.g. $P(OR)_3$, $(CH_3)_2S$) is a method of forming carbonyl groups. The ozonolysis of an enol ether such as **51** should give an aldehyde and a formate ester. When the enol ether **51** was treated with O_3 (CH_2Cl_2/CH_3OH, 9:1) β-hydroxyaldehyde **19** was obtained rather than the expected β-formylaldehyde **56**. The absence of **56** in the crude product from the ozonolysis may be due to the methanol present in the solvent system used. Methanol is added to the reaction to trap the decomposition product of the primary ozonide as its hydroperoxide **57**.[21] In this case, however, reductive cleavage of the hydroperoxide presumably forms alcohol **19**, not formate **56**.

When the ozonolysis of the enol ether **51** was carried out in Skellysolve B/dichloromethane followed by reductive



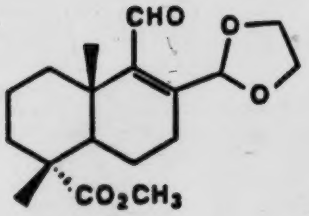
56



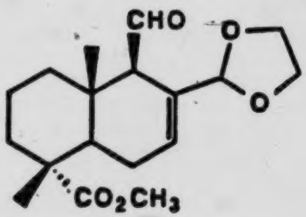
57

work-up ($P(OCH_3)_3$), formate **56** was isolated. The hrms of **56** has a peak at m/z 368 ($C_{19}H_{28}O_7$) corresponding to the molecular ion. This was confirmed by the cims which shows a peak for M + 18 at m/z 386 (100%). The ^1H nmr spectrum of **56** displays a one proton doublet at δ9.86 (2.5 Hz, H-11), a one proton singlet at δ8.24 characteristic of the formyl group, and a one proton doublet at δ2.88 (2.5 Hz, H-9). All these data are consistent with the proposed structure **56**.

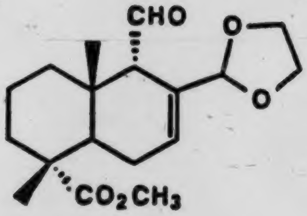
Compound **56** is an attractive intermediate since the C-8 oxygen has been converted to a good leaving group. Introduction of the ring B double bond was achieved by β-elimination of the formate by treatment with DBU. When the crude product from the ozonolysis of enol ether **51** was treated with DBU in benzene under reflux, a mixture of four compounds was formed. These were identified as compounds 53, 58, 52, and 19. The ratio of products was dependent on the reaction conditions (ratios were determined by ^1H nmr). When short reaction times were used aldehydes 53 and 58 were the major components of the mixture. With longer reaction times the amount of the aldehyde 52 in the reaction mixture increased. The hydroxyaldehyde 19 was almost always present in small amounts (*ca.* 10%). These observations are in agreement with the comment that compound 52 is formed from 53 under strongly basic conditions.



53



58



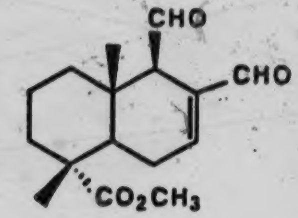
52

Compounds 19 and 52 were identified as described previously. The α,β-unsaturated aldehyde 53 was identified as follows. The ir spectrum of 53 shows absorption bands for the ester (1725 cm^{-1}) and conjugated aldehyde (1680 cm^{-1}). Its hrms shows a strong peak at m/z 322 (72%) corresponding to the molecular formula $C_{18}H_{26}O_5$, with a fragment ion at m/z 293 (5%) for $C_{17}H_{25}O_4$ (M$^+$ -

CHO). The ^{1}H nmr spectrum of 53 shows a one proton singlet at δ10.08 for the aldehydic proton and a singlet at δ5.82 for the H-12 proton. The remaining signals in the ^{1}H nmr spectrum are in agreement with the structure 53.

Compound 58 shows the following spectroscopic characteristics. Its hrms has a peak for the molecular ion ($C_{18}H_{26}O_5$) at m/z 322 (13%), and fragment ions at m/z 294 (39%) and 293 (35%) corresponding to M^+ - CO and M^+ - CHO, respectively. Its ^{1}H nmr spectrum displays one proton signals at δ9.57 (d, 5.5 Hz) for the aldehyde, at δ6.14 (ddd, 5.5, 2.5, 2 Hz) for the vinyl proton, and δ2.80 (dddd, 5.5, 4, 2.5, 2 Hz) for H-9. Decoupling experiments show that H-9 (δ2.80) has long range couplings with the vinyl proton and both protons at C-6. Comparison of the spectroscopic data for 52 with that of 58 indicate that 52 and 58 are C-9 epimers, therefore compound 58 has the C-9 CHO group in the β-orientation.

Deprotection of 58 with p-TsOH in acetone gave the dialdehyde 59. The ir spectrum of 59 shows absorption bands for carbonyls (1723, 1679 cm^{-1}) and an olefin (1642 cm^{-1}). Its hrms shows the molecular ion ($C_{16}H_{22}O_4$) at m/z 278 as a weak peak (2%). The ^{1}H nmr spectrum of the dialdehyde 59 displays signals for two quaternary methyl groups (δ1.31 and δ0.99), a methoxyl group (δ3.69), a vinyl proton (δ7.08, ddd, 5.5, 2, 2 Hz), and two aldehydic protons (δ9.54, d, 4 Hz and δ9.46, s). The chemical shifts of the ene dialdehyde system in 59 are similar to those reported for polygodial (3),[10] supporting the relative stereochemical assignment of 58.



59

With the unsaturated aldehydes 52, 53, and 58 in hand, we investigated methods to introduce the C-9 hydroxyl group. The most appropriate way to carry out the hydroxylation step with our intermediates is by treatment of the formed enolate at C-11 with a peroxide. Hydroxylation under these conditions occurs at C-9.

Vedejs and coworkers[47] have described the direct hydroxylation of enolates with the molybdenum peroxide reagent MoO_5•pyridine•HMPA (MoOPH). Others have used this reagent to introduce the hydroxyl group at C-9 in their synthesis of warburganal.[8,9,48] In each case the reaction was performed on intermediates very similar to our unsaturated aldehydes and the product obtained showed that the reaction proceeded with a high degree of stereoselectivity.

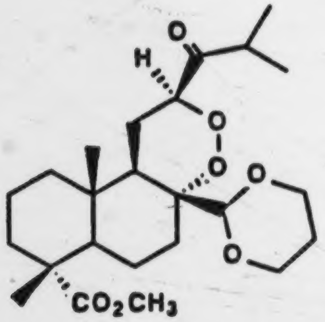
When the isomeric mixture of aldehydes 52, 53, and 58 was treated under the reaction conditions described by Vedejs[47] (lithium diisopropylamide (LDA)/hexane/THF, MoOPH) only starting material was isolated. Treatment of the mixture of aldehydes with LDA (from a stock solution as described by Vedejs or prepared in situ) followed by kinetic protonation (0.5 M H_2SO_4/H_2O) gave disappointing results. When 1.5-3 eq. of LDA was used at different temperatures (-78° - -8°C) only starting aldehydes 52, 53, and 58 were obtained in the same ratio as in the starting material. A complex mixture of products was formed when 5-10 eq. of LDA was employed.

The results of the deprotonation with LDA were unexpected. In two of the syntheses reported, good yields were obtained in the hydroxylation step, although here the C-8 CHO is protected as its dioxane.[8,9] However, in the other synthesis with a C-8 dioxolane protecting group, a low yield is reported for this hydroxylation.[48] We hoped that protecting the C-8 aldehyde as its dioxane would give better results in this reaction. The introduction of the dioxane protecting group was carried out on compound 27

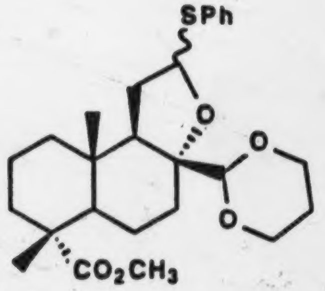
Ketoaldehyde 27 was protected with 1,3-propanediol under mild conditions to obtain compound 60. The hrms shows a molecular ion at m/z 438 ($C_{24}H_{38}O_7$) corresponding to the molecular formula. The ^1H nmr spectrum of 60 is in agreement with the proposed structure. In particular H-14 in 60 appears as a singlet at δ4.81.

The transformation of the ketoperoxide 60 to the unsaturated aldehydes 63 was carried out as described in the dioxolane series. Compound 60 was reduced to the corresponding alcohol ($NaBH_4/CH_2Cl_2/MeOH$), followed by heterolytic fragmentation ($NaOCH_3/CH_3OH$) and hemithioacetal formation (thiophenol/TFA/CH_2Cl_2) to obtain compound 61. The ir spectrum of the hemithioacetals 61 shows absorption bands for a monosubstituted benzene (1596, 738, and 690 cm^{-1}). The cims of 61 has a peak at m/z 478 corresponding to the molecular ion (460) plus ammonia.

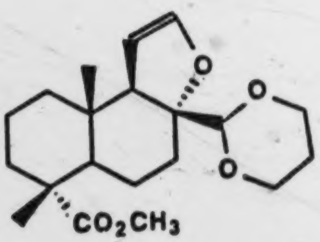
The hemithioacetals 61 were oxidized with m-CPBA and the resulting sulfoxides were pyrolyzed ($P(OEt)_3$/xylenes, reflux) to obtain the enol ether 62. The hrms of compound 62 presents a peak for the molecular weight at m/z 350 ($C_{20}H_{30}O_5$). The ^1H nmr spectrum of the enol ether 62 shows the vinyl protons at δ6.45 (t, 3 Hz) and δ5.16 (m). Oxidative cleavage of the enol ether 62 ((1) O_3, (2) $P(OCH_3)_3$) followed by β-elimination of the formate afforded the unsaturated aldehydes 63. The ^1H nmr of 63 displays three aldehydic proton signals for the isomeric unsaturated aldehydes: δ10.08 (s), δ9.68 (d, 4.5 Hz), and δ9.62 (d, 5 Hz).


H
O
O
O
O
O
CO₂CH₃

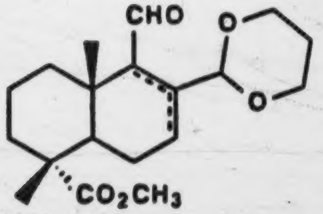
60


SPh
O
O
O
CO₂CH₃

61



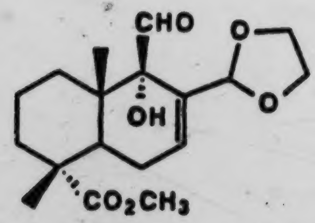
62


CHO
O
O
CO₂CH₃

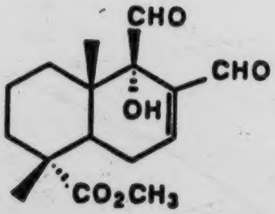
63

When the isomeric unsaturated aldehydes 63 were treated with LDA (hexane/THF, -78°C) followed by quenching with MoOPH (-78 → 0°C) only starting material was recovered. Treatment of 63 with LDA (THF, -78°C) followed by addition of a 0.5 *M* H_2SO_4 solution did not cause any change in the ratio of the aldehydes. The use of hexamethylphosphoramide (HMPA) as co-solvent in the attempted deprotonation-protonation sequence gave the same results.

Because of the inertness of the unsaturated aldehydes 52, 53 and 58 or 63 to enolate formation with LDA, we decided to attempt the reaction using potassium hydride (KH) as the base. Addition of the aldehydes 52, 53 and 58 to a suspension of KH in THF, followed by addition of MoOPH (-78 → 0°C) afforded compound **64** as the major product. The hydroxyaldehyde **64** shows an absorption band for an hydroxyl group (3450 cm^{-1}) in its ir spectrum. The ^{1}H nmr spectrum of **64** is consistent with the assigned structure, in particular, it displays an aldehydic proton at δ9.83 (d, 1 Hz), a vinyl proton at δ6.29 (dd, 5.25, 2.5 Hz), and an hydroxyl proton at δ3.92 (d, 1 Hz). Addition of D_2O causes the loss of the δ3.92 signal and the signal at δ9.83 now appears as a singlet.



64



20

Removal of the protecting group in compound **64** under standard conditions (p-TsOH/acetone) afforded 4αmethoxycarbonylwarburganal (**20**). Recrystallization of the product afforded crystals with m.p. 101-102°C, and $[\alpha]_D$ -135° (c 0.1, $CHCl_3$) [reported[8] m.p. 104-105°C, $[\alpha]_D$ -132° (c 1.11, $CHCl_3$)]. The hrms of **20** shows a molecular ion at m/z 294 corresponding to the molecular formula $C_{16}H_{22}O_5$. Its ^1H nmr spectrum displays signals for two quaternary methyls (δ1.33 and δ1.13), and one methoxyl group (δ3.70). The following signals are similar to those reported for warburganal (**1**):[10] The C-9 CHO at δ9.77 (1.5 Hz) as a doublet, the C-8 CHO at δ9.44 as a singlet, the vinyl proton at δ7.22 (5, 2.5 Hz) as a doublet of doublets, and a D_2O exchangeable proton at δ4.12 (d, 1.5 Hz). All these data are consistent with the structure proposed for 4α-methoxycarbonylwarburganal (**20**).

In order to complete the synthesis of warburganal (**1**), it was now necessary to perform this reaction sequence on the compound in which the carboxylate function has been transformed to a methyl group.

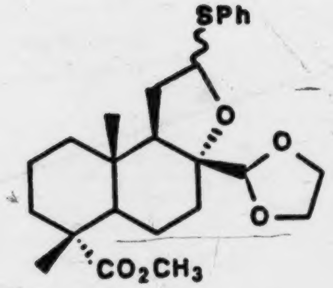
3. Reduction of the Carboxyl Group to a Methyl Group: Synthesis of Warburganal (1)

In order to use this synthetic plan for the synthesis of warburganal, the methyl ester functionality must be converted to a methyl group. The intermediate chosen for this conversion should be one in which functional groups other than the ester are either protected or relatively unreactive. We chose the hemithioacetals 47 and 48, which have the functional groups protected as the corresponding acetals, as the starting point for the methyl ester conversion.

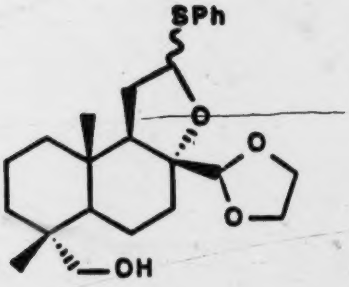
Most methods reported for the transformation of an ester group to a methyl group consist of two or more steps. These transformations proceed through the intermediate alcohol and/or aldehyde which may be further reduced to the methyl group under a wide variety of conditions.

Reduction of the methyl ester 65 (epimeric mixture at C-12) with lithium aluminum hydride ($LiAlH_4$) in ethyl ether gave the primary alcohols 66 in 92% yield. The ir spectrum of 66 does not show the characteristic absorption band for an ester, but displays a broad band at 3436 cm^{-1} corresponding to an hydroxyl group. Its ^1H nmr spectrum is consistent with the structure assigned, in particular, it displays the protons geminal to the hydroxyl group as doublets (δ3.37, 11 Hz and δ3.11, 11 Hz).

The primary alcohols 66 were oxidized with pyridinium chlorochromate (PCC) in dichloromethane[49] to afford aldehyde 67. The ir spectrum of 67 shows absorption bands for an aldehyde group (2680, 1723 cm^{-1}). Its hrms has a



65

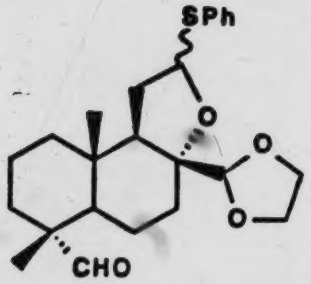


66

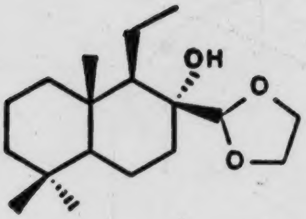
peak at m/z 416 corresponding to the molecular ion ($C_{24}H_{32}O_4S$). The ^1H nmr spectrum of **67** displays singlets for the aldehydic protons (δ9.22 and δ9.17, one for each of the C-12 epimers).

An aldehyde may be reduced to a methyl group under different reaction conditions.[50] Methods that use basic conditions were the more appropriate in our case because of the acid-labile acetal functional groups on **67**. Hydrazone derivatives are normally reduced under these conditions and thus the Wolff-Kishner reaction was chosen for this transformation.

Treatment of the aldehydes **67** under the conditions of the Huang-Minlon modification of the Wolff-Kishner reaction[51] ($KOH/H_2NNH_2/(HOCH_2CH_2)_2O$, 210°C) gave a mixture of compounds in which alcohol **68** was present as the major component.



67

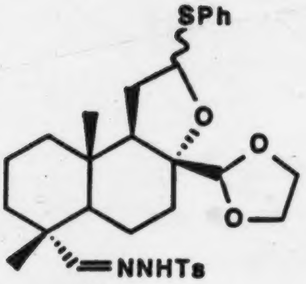


68

The ir spectrum of 68 shows absorption bands for hydroxyl (3565 cm^{-1}) and the characteristic doublet for gem-dimethyl[52] (1387 and 1364 cm^{-1}). Its molecular weight (m/z 296) was confirmed by cims (m/z 314 (M^+ + 18)). The ^1H nmr of compound 68 displays three quaternary methyls (δ0.87, 6H and δ0.81, 3H), the protons of the dioxolane group (δ5.1, s, 1H and δ4.13-3.85, m, 4H), a D_2O exchangeable proton (δ2.67, s), a one proton complex signal centered at δ1.99, and a triplet at δ1.01 (7.5 Hz, 3H). Irradiation of the signal at δ1.99 collapsed the triplet at δ1.01. The spectral data indicates that the thiophenol moiety and the aldehyde group present in 67 have been replaced in compound 68 by methyl groups, one quaternary and the other part of an ethyl group. Presumably the methyl groups are formed by reduction of the corresponding aldehydes.

Milder reaction conditions were needed in the reduction of the aldehyde to methyl to avoid the removal of the thiophenol moiety. Two different laboratories have reported reduction reaction conditions which use a stronger base (KO^tBu) than potassium hydroxide and lower temperatures. Both methods give good results and they differ only in the solvent used in the reaction. When the aldehydes **67** were treated with hydrated hydrazine (cat. amount Et_3N/EtOH, reflux)[53] a colorless oil was obtained. Treatment of the crude product with potassium *tert*-butoxide in refluxing toluene[54] afforded two less polar products (by tlc) that were purified by chromatography. The ^1H nmr spectrum of each of the products shows the absence of the characteristic signal for the aldehyde group, indicating that the reaction did take place, but each of the products was an inseparable mixture of epimers. When the aldehydes **67** were treated under the reaction conditions as described above, but using dimethylsulfoxide (DMSO, 70°C) as solvent,[55] the same products were obtained.

Tosylhydrazones have also been reduced in different ways to the corresponding alkane. Treatment of the aldehydes **67** with tosylhydrazide (refluxing EtOH) afforded the tosylhydrazone **69**.

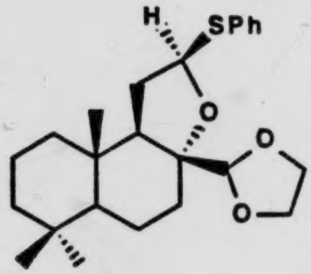


69

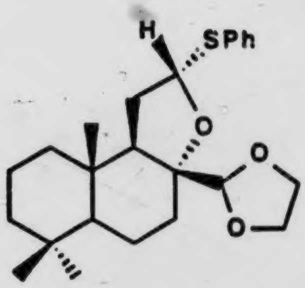
The ir spectrum of 69 shows absorption bands characteristic of the sulfonamide at 3196 and 1169 cm^{-1}.[56] The highest mass peak in the hrms of 69 is a fragment ion at m/z 511 ($C_{28}H_{35}N_2O_3S_2$) corresponding to the molecular ion minus the dioxolane ($C_3H_5O_2$).

Treatment of compound 69 with an excess of $NaBH_4$ in refluxing methanol[57] followed by purification afforded two major fractions. The ^1H nmr spectrum of each fraction indicates that each is a complex mixture.

Kabalka and coworkers[58] have reported the reduction of tosylhydrazones with boranes. Reduction of 69 with bis(benzoyloxy)borane ($CHCl_3$) at 0°C, followed by addition of $NaOAc \cdot 3H_2O$ and DMSO, then heating under reflux afforded the hemithioacetals 70 and 71. The overall yield was 46% from the aldehydes 67. The use of (n-Bu)$_4$NOAc[59] instead of $NaOAc\cdot 3H_2O$ did not improve the yield. Similar results are obtained with catecholborane.[60]



70



71

The ir spectrum of **70** has the characteristic gem-dimethyl bands (1390 and 1380 cm^{-1}). The hrms shows an ion peak at m/z 402 corresponding to the molecular formula $C_{24}H_{34}O_3S$. The ^1H nmr spectrum of **70** displays signals for three quaternary methyls (δ0.98, δ0.87, δ0.84) and shows H-12 as a doublet of doublets at δ5.56 (9, 6 Hz). The ^{13}C nmr spectrum of **70** shows signals for methyl groups at δ33.4, δ20.9, and δ15.9 (C-18, C-19, and C-20, respectively). The chemical shift of the methyls is similar to that reported for natural products with the 4α,4β,10-trimethyldecaline system.[61] These data are in agreement with the structure proposed for compound **70**.

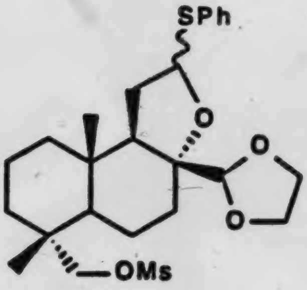
The hemithioacetal **71** has ir and ms very similar to those of **70**. The ^1H nmr spectrum of **71** confirms the proposed structure, in particular the three singlets for quaternary methyls (δ0.89, δ0.84, δ0.80) and H-12 as a doublet of doublets (δ5.60, 8, 1.5 Hz). The ^{13}C nmr displays signals for three methyl groups (δ33.4, δ20.9, and δ15.8).

The conversion of the methyl ester 65 to the gem-dimethyl compounds 70 and 71 was achieved under mild conditions. The yields are high except for the step involving the reduction of the tosylhydrazone 69. Attempts to increase the yield in this last reaction were unsuccessful.

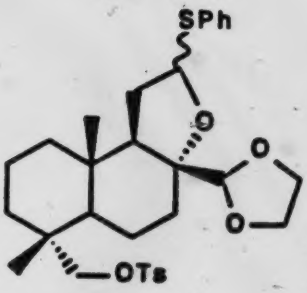
A different approach to the reduction of the ester group to methyl was investigated. Derivatives of alcohols may be reduced to the alkane by S_N2 displacement with hydride or by homolytic cleavage of the C-O bond.[62a] The radical deoxygenation method does not normally give high yields with primary alcohol derivatives[62b] whereas the S_N2 displacement method usually gives good yields. However, the displacement method sometimes fails with neopentyl derivatives such as the alcohols 66.

We decided to try the displacement method employing the sulfonates of 66. Treatment of the alcohols 66 with mesyl chloride (Et_3N/CH_2Cl_2) afforded the mesylates 72 as a yellow oil. The ^1H nmr spectrum of 72 displays the methyl group of the sulfonates at δ3.14 and δ3.02 (one for each epimer). When a solution of the mesylate 72 and lithium triethylborohydride ($LiEt_3BH$)[63] in THF was refluxed for 40 h, the alcohols 66 were isolated as the only product of the reaction.

Formation of the tosylates 73 was carried out by mixing the alcohols 66, p-toluenesulfonyl chloride (tosyl chloride, TsCl), and 4-dimethylaminopyridine in pyridine. The ir spectrum of 73 shows absorption bands for sulfonates (1359, 1176 cm^{-1})[38] and its hrms has a molecular ion peak at m/z 572 which corresponds to the molecular formula $C_{31}H_{40}O_6S_2$. The ^1H spectrum of 73 is in agreement with the proposed structure.



72



73

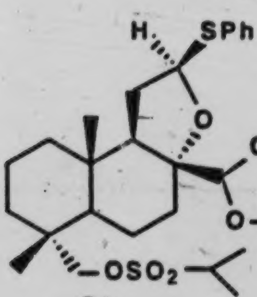
When the tosylates 73 were heated in refluxing THF in the presence of $LiAlH_4$, the alcohols 66 were isolated from the reaction mixture as the only product. However, the use of the more powerful nucleophilic hydride, lithium triethylborohydride, gave better results.[64] A mixture of the tosylate 73 and a five-fold excess of $LiEt_3BH$ in refluxing THF yielded the alcohols 66 and the reduced hemithioacetals 70 and 71 in a ratio of 2.5:1 (after purification). The use of 1,2-dimethoxyethane or benzene as the solvent at refluxing temperatures gave a 3:1 ratio of the alcohols 66 and hemithioacetals 70 and 71 respectively.

In this case, S-O cleavage occurred in preference to C-O cleavage because of the hindered nature of the neopentyl sulfonates 72 and 73. It has been reported that more bulky sulfonates (e.g. tosylate) promote C-O cleavage with hydrides. Hua and coworkers[65] have reported that 2-propanesulfonate derivatives of hindered alcohols are readily displaced by hydride. The bulky isopropylsulfonate gave better yields in the reaction than the corresponding tosylate or mesylate derivatives.

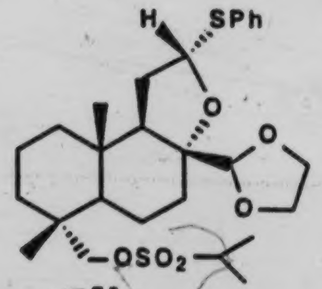
2-Propanesulfonyl chloride was prepared by oxidation of 2-propanethiol with chlorine in water.[66] Treatment of the alcohols 66 with 5 eq. of 2-propanesulfonyl chloride (Et_3N/Et_2O, -20°C for 2 h)[67] afforded the sulfonates 74 and 75 in 85% yield. An excess of sulfonyl chloride and low temperatures are important in order to obtain a good yield in this reaction.

The ir spectrum of 74 shows absorption bands characteristic of sulfonates (1350 and 1156 cm^{-1}).[38] The

^{1}H nmr spectrum of **74** displays the signals expected for this structure, in particular, the signals for the isopropyl group at δ3.31 (quintet, 6.5 Hz, 1H) and at δ1.44 (d, 6.5 Hz, 6H). The α-epimer **75** has very similar spectroscopic data to that of **74**.



74

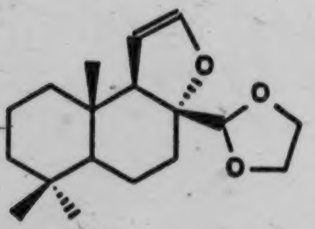


75

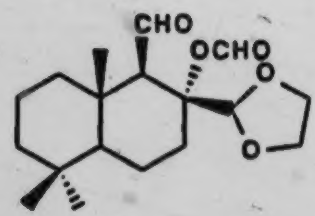
Treatment of the sulfonates **74** and **75** with lithium triethylborohydride (toluene, 90°C, 12 h) afforded the hemithioacetals **70** and **71** in 64% yield. The spectroscopic data for the hemithioacetals **70** and **71** from this reaction were identical to those obtained from the reduction of the tosylhydrazones **69**. The hydride displacement route gave a slightly better overall yield than the route involving the tosylhydrazone. Although the yield of this reaction sequence is modest, it is reasonable since it involves reduction at a neopentyl carbon.

Having the hemithioacetals **70** and **71** in hand, the synthesis of warburganal (**1**) was completed using the same reaction sequence developed for the synthesis of 4α-methoxycarbonylwarburganal (20).

The hemithioacetals 70 and 71 were oxidized with m-CPBA (ca. 1 eq.) to give the corresponding sulfoxides. A solution of the sulfoxides, and triethylphosphite (5 eq.) in xylenes was refluxed for 4 h to afford the enol ether 76 after chromatography. The ir spectrum of 76 shows the characteristic absorption band for Δ^2-dihydrofurans (1592 cm^{-1}).[33] Its hrms has an ion at m/z 292 which corresponds to the molecular ion ($C_{18}H_{28}O_3$). The ^1H nmr spectrum of 76 displays signals for three quaternary methyls (δ1.05, δ0.89, δ0.84) and one proton signal for vinyl protons at δ6.47 (t, 3.5 Hz) and δ5.39 (m).



76

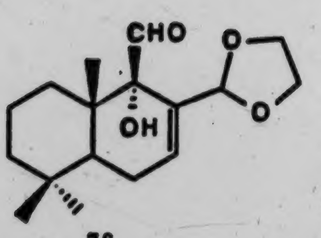


77

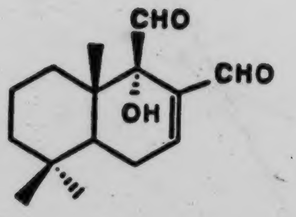
Treatment of the enol ether 76 with ozone (EtOAc, -78°C), followed by addition of trimethylphosphite (-78° → r.t.) gave the corresponding β-formylaldehyde 77. The ^1H nmr of the crude 77 displays signals for the aldehydic proton (δ9.88, d, 3 Hz), formyl proton (δ8.24, s) and three quaternary methyls (δ1.29, δ0.90, δ0.85). When a solution of the crude formate 77 and DBU in benzene was refluxed, a mixture of unsaturated aldehydes was obtained. The unsaturated aldehydes were treated with KH (THF, 5°C), followed by addition of the peroxide MoOPH (-78 → 0°C) to give α-hydroxyaldehyde 78. It was expected that the bulky oxidizing reagent would approach from the less hindered α face (as observed previously) and this expectation was confirmed by the formation of warburganal (1).

The hrms of compound 78 shows the molecular ion at m/z 294 corresponding to $C_{17}H_{26}O_4$. The ir spectrum of 78 has absorption bands for hydroxyl (3460 cm^{-1}), aldehyde (1713 cm^{-1}) and for the gem-dimethyl group (1387, 1362 cm^{-1}). Its ^1H nmr spectrum displays signals corresponding to three quaternary methyls (δ1.22, δ0.97, δ0.91), an hydroxyl proton at δ3.90 (d, 1 Hz, D_2O exchangeable), a vinyl proton at δ6.36 (dd, 5, 2.5 Hz), and an aldehydic proton at δ9.85 (d, 1 Hz). These data are in agreement with the structure of the α-hydroxyaldehyde 78.

Removal of the dioxolane protecting group (p-TsOH/acetone) afforded warburganal (1) showing m.p. 106-107°C and $[\alpha]_D$ -243° (c 0.037, $CHCl_3$) [reported[8] $[\alpha]_D^{25}$ -263° (c 0.38, $CHCl_3$)]. The spectroscopic data for 1 (ir,



78



1

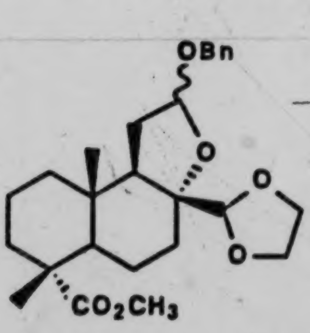
^{1}H nmr, ^{13}C nmr, hrms) are similar to those reported for synthetic[10] and natural[2] warburganal.

4. Ring A Transformations: Towards the Synthesis of Muzigadial (2)

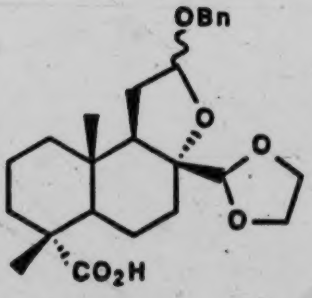
Once the transformation of levopimaric acid (17) to warburganal (1) was achieved, we turned our attention to the synthesis of muzigadial (2). The same sequence of transformations used in the synthesis of warburganal are required for the synthesis of muzigadial except in the modification of ring A where to introduce a β-methyl group at C-3 and an exocyclic olefin at C-4.

For the same reasons as before, we chose the hemiacetal 45 as the starting material for the transformation of ring A. The hemiacetal moiety was protected as the corresponding acetal with benzyl alcohol (TFA/CH_2Cl_2) to provide the acetals 79. The α-epimer at

C-12 was present as the major component of the mixture (*ca.* 85%). An analytical sample of 79-α was obtained by recrystallization (m.p. 137-138°C). The hrms of 79-α displays a fragment ion at m/z 371 ($C_{23}H_{31}O_4$, $M^+ - C_3H_5O_2$) and a benzylic ion at m/z 91 (C_7H_7, 100%). Its ^1H nmr spectrum displays a complex signal for the aromatic protons at δ7.38-7.22 (5H), a one proton doublet assigned to H-12 at δ5.25 (6 Hz), and the benzylic protons at δ4.8 (d, 11.5 Hz) and δ4.46 (d, 11.5 Hz). The other signals in the ^1H nmr spectrum of 79-α are in agreement with its structure.



79



80

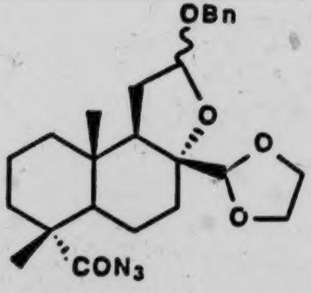
In order to form the exocyclic double bond at C-4 we must remove the C-4 carboxylate group. There are several methods reported for the removal of the carboxylic acid group with concomitant formation of an olefin between the carbons α and β to the group.

Hydrolysis of the methyl ester 79 was carried out with "anhydrous hydroxide" ($H_2O/KO^tBu/THF$)[68] to afford the acid 80. The ir spectrum of 80 shows the bands characteristic of a carboxylic acid (3520-2240 and 1693 cm^{-1}). The signal characteristic of the methoxyl group of the ester (δ3.62, s) is not present in the ^1H nmr spectrum of 80.

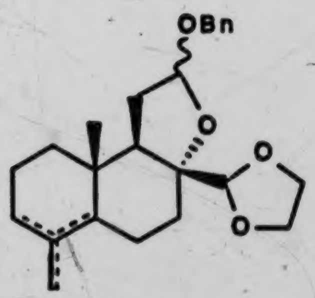
Zeiss and Martin[69] have reported decarboxylation and olefin formation on a diterpene acid by the Curtius degradation followed by Hofmann elimination. When they performed these transformations on dehydroabietic acid the exocyclic olefin was the major component of the isomeric mixture of products.

Treatment of the acid 80 with $SOCl_2$ (Et_2O) followed by sodium azide (acetone, 5°C) afforded the corresponding acyl azide 81. The ir spectrum shows absorption bands for an acyl azide group (2134 and 1704 cm^{-1}). Compound 81 was heated at 140° (xylenes) for 36 h and the resulting product was reduced with $LiAlH_4$ to afford a basic compound. Attempts to isolate the expected secondary amine failed. Treatment of the crude product from the reduction with methyl iodide (K_2CO_3/EtOH, reflux) afforded, after purification, a mixture of isomeric olefins 82 (*ca.* 10% from 80).

The ^1H nmr spectrum of 82 displays two methylene singlets (δ4.67 and δ4.43) and three singlets (δ0.95, δ0.73, δ0.65) for the angular methyl (C-10 CH_3) indicating the presence of 3 different isomers. Integration of the C-10 CH_3 singlets shows that the signal at δ0.65 is that of the major component of the isomeric mixture and this chemical shift is reasonable for the angular methyl of the exocyclic olefin isomer. The low yield obtained for 82 discouraged us from using this sequence of reactions to form the exocyclic olefin.

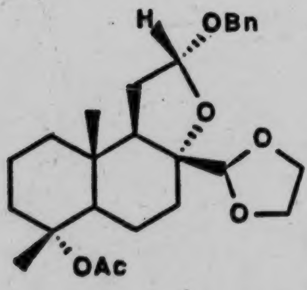


81

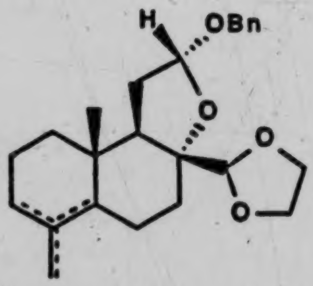


82

When the C-12 α epimer of 80 was treated with lead tetraacetate (pyridine/benzene, reflux), the acetate 83 and the isomeric olefins 84 were isolated in 24% and 17% yield respectively. The ir spectrum of 83 shows absorption bands for acetate (1727 and 1248 cm^{-1}). Its hrms shows fragment ions at m/z 371 ($C_{23}H_{31}O_4$) corresponding to the molecular ion minus $C_3H_5O_2$ and at m/z 311 ($C_{21}H_{27}O_2$) for the molecular ion minus the dioxolane and acetate unit ($C_5H_9O_4$). The ^1H nmr spectrum of 83 is consistent with its structure, in particular, it displays singlets at δ1.93 for the acetyl methyl and δ1.41 for the C-4 CH_3 group. NOe experiments were used to assign the relative stereochemistry at C-4. In the ^1H nmr of 83, presaturation of the signal at δ0.91 (angular methyl group) resulted in a 16% enhancement in the signal at δ1.41. This indicates that the C-4 CH_3 is close to the C-10 CH_3 and therefore the C-4 CH_3 possess a β orientation.



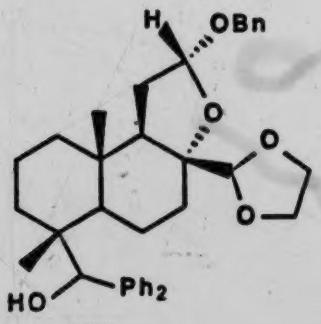
83



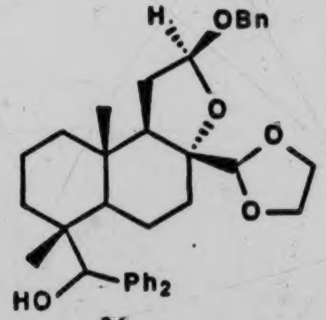
84

The isomeric mixture 84 was characterized as follows. Its ir spectrum shows an absorption band at 1650 cm^{-1} indicative of the presence of an olefin. Its ^1H nmr spectrum displays signals for an exocyclic olefin (δ4.71 and δ4.46) and the angular methyl group (mixture of isomers at δ0.99, δ0.78 and δ0.69, ratio of 1:2:2.3 respectively). The use of lead tetraacetate for the decarboxylation-olefin formation had thus resulted in poor selectivity and a low yield of the olefins.

Matsumoto and coworkers[70] have reported the formation of the C-4 exocyclic olefin of a substituted methyl abietate by treatment of the corresponding diphenylcarbinol with $Pb(OAc)_4$. Compound 79 was treated with phenyllithium (Et_2O, -5°C). The alcohols 85 and 86 were obtained and separated by column chromatography.



85



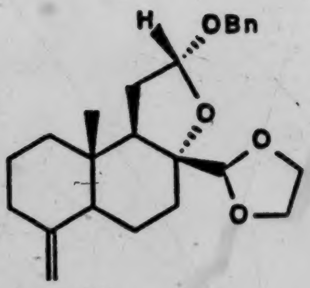
86

Alcohol 85 was identified as follows. Its ir spectrum shows an absorption band for hydroxyl (3460 cm^{-1}). Its hrms has a fragment ion at m/z 495 ($C_{34}H_{39}O_3$) which corresponds to the molecular formula minus $C_3H_5O_2$. The ^1H nmr spectrum of 85 is consistent with the assigned structure, in particular, it displays complex signals for the aromatic protons (δ7.81, δ7.5, and δ7.38-7.14), a doublet for H-12 (δ5.19, 6 Hz) and a D_2O exchangeable singlet for the hydroxyl (δ2.44). The alcohol 86 displays very similar spectroscopic data to those of 85. The β orientation at C-12 of the benzyl group of 86 was assigned on the basis of the multiplicity of the H-12 signal (δ5.19, t, 6 Hz) observed in its ^{1}H nmr spectrum.

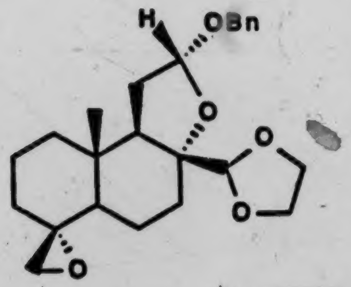
The next sequence of reactions was carried out with the C-12 α epimer because of the ease of identification of the corresponding products. Compound 86 was epimerized by treatment with benzyl alcohol (TFA/CH_2Cl_2) to give 85 as the major component of the product mixture.

When alcohol 85 was treated with $Pb(OAc)_4$ (benzene, 40°C) in the presence of calcium carbonate an isomeric mixture of olefins 84 was isolated in 77% yield. The ^{1}H nmr spectrum of 84 shows the angular methyl of each of the $\Delta^{3,4}$, $\Delta^{4,5}$, $\Delta^{4(18)}$ isomers at δ0.98 (4%), δ0.76 (11%) and δ0.68 (85%) respectively. The exocyclic olefin 23 (δ0.68, C-10 CH_3) is present as the major component in the mixture. A pure sample of 23 was obtained from the photooxygenation of 84 as described below. The hrms of 23 has a fragment ion at m/z 311 ($C_{21}H_{27}O_2$, $M^+ - C_3H_5O_2$). The molecular formula ($C_{24}H_{32}O_4$) was confirmed by elemental analysis. The ^{1}H nmr spectrum of 23 displays the olefinic protons as one proton doublets at δ4.70 (1.5 Hz) and δ4.44 (1.5 Hz) and the angular methyl group as a singlet at δ0.70 (3H). Other signals in the ^{1}H nmr spectrum are in agreement with the assigned structure for 23.

Having found a method for forming the exocyclic olefin at C-4 with good selectivity, we turned our attention to the introduction of the methyl group at C-3



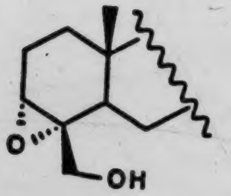
23



87

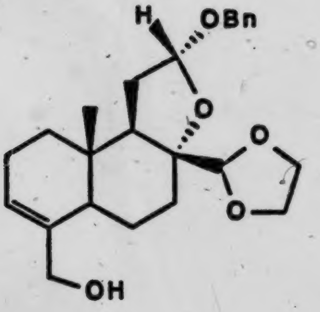
with the required β orientation. We thought that introduction of the methyl group could be accomplished by displacement of a leaving group attached to C-3 from the α face. Such a transformation could possibly be achieved with a compound such as the hydroxyepoxide shown in Figure 3. The diol resulting from the ring opening of the epoxide could then be converted to an exocyclic olefin in one of the later steps of the synthesis. Introduction of the hydroxyepoxide functionality as depicted in Figure 3 was accomplished[71] as follows. Treatment of 84 with m-CPBA (CH_2Cl_2, r.t.) afforded an isomeric mixture of epoxides. The spiro epoxide 87 was isolated from the mixture and identified. The hrms of 87 shows a fragment

Figure 3. Hydroxyepoxide.

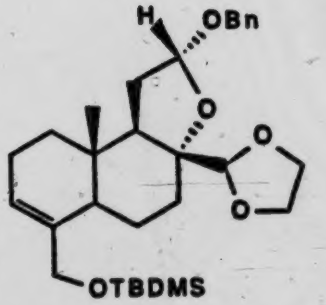


ion at m/z 327 ($C_{21}H_{27}O_3$) corresponding to the molecular ion with the loss of the dioxolane fragment ($C_3H_5O_2$). The ^{1}H nmr of 87 is consistent with the assigned structure, in particular it displays the protons of the oxirane ring at δ2.74 (dd, 4.5, 1.5 Hz) and δ2.57 (d, 4.5 Hz). The relative stereochemistry at C-4 was assigned by assuming that the epoxide formed is that resulting from the attack of the peracid from the less hindered side of the olefin. The stereochemical assignment was confirmed at a later stage of the synthesis.

Attempts to convert the epoxide 87 to the allylic alcohol 88 under standard conditions (Et_2NLi)[72] failed. The use of LDA (Et_2O, r.t.) afforded a complex mixture. Generation of bromomagnesium isopropylcyclohexylamide (MICA) (isopropylcyclohexylamine/EtMgBr, THF, reflux) followed by addition of a solution of the mixture of epoxides in THF (40°C, 18 h)[73] yielded the allylic alcohol 88 after purification. The ir spectrum of 88 shows an absorption band corresponding to an hydroxyl (3450 cm^{-1}). The ^1H nmr spectrum of 88 displays a signal for the vinylic proton (δ5.6, m) and a one proton triplet for the hydroxyl (δ1.15, 6 Hz, D_2O exchangeable). The other signals in the ^1H nmr spectrum are in agreement with the structure 88.



88



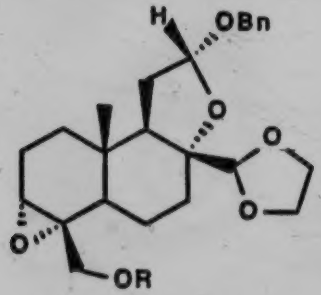
89

Attempts to form 88 in one step by photooxygenation[74] of the isomeric mixture of olefins 84 failed. An ethanolic solution of 84 containing rose bengal was irradiated with light at room temperature for 96 h while oxygen was bubbled through the solution. Purification of the reaction mixture led to isolation of a pure sample of the exocyclic olefin 23. Presumably compound 23 is not reactive under these reaction conditions while the other two isomers do undergo reaction.

Treatment of the crude alcohols from the ring opening reaction with tert-butyldimethylchlorosilane (TBDMSCl) (iPr$_2$NEt/dimethylformamide (DMF))[75] followed by column chromatography gave the protected alcohol 89 in 20% overall yield from 87. Its hrms shows an intense fragment ion at m/z 441 ($C_{27}H_{41}O_3Si$) corresponding to the molecular ion minus the dioxolane fragment ($C_3H_5O_2$). The ^{1}H nmr spectrum of 89 shows a complex signal for the vinyl proton (δ5.55), a one proton doublet for one of the allylic protons (δ4.11, 13.5 Hz), and singlets for methyls of the protecting group (δ0.93, 9H and δ0.08, 6H).

Epoxidation of the olefin 89 with m-chloroperbenzoic acid in dichloromethane at room temperature afforded the epoxide 90 as the only product in 89% yield. The hrms of 90 has a fragment ion at m/z 473 ($C_{26}H_{37}O_6Si$) corresponding to the molecular ion minus the tert-butyl group (C_4H_9). Its ^{1}H nmr spectrum is consistent with the assigned structure, in particular, it displays the geminal allylic protons at C-18 as two doublets (δ3.9, 11 Hz and δ3.4, 11 Hz), H-3 as a doublet (δ3.11, 3 Hz) and signals characteristic of the protecting group (δ0.89, 9H, δ0.05, 3H, and δ0.04, 3H). The α orientation was assigned to the epoxide by assuming that the peracid approaches the olefin from the less hindered α-face of the molecule.[71]

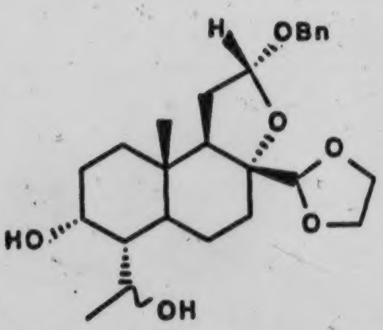
We were now ready to introduce a β-methyl group. Opening of epoxides with organocopper reagents is a well established method of C-C bond formation.[76] When compound 90 was treated with 10 eq. of lithium dimethylcuprate (Et$_2$O, r.t.) only the starting material was isolated. Treatment of 90 with the higher order organocopper reagents $(CH_3)_2Cu(CN)Li_2$ gave the same result (Et$_2$O, r.t.).[77] Treatment of epoxide 90 with excess of methylmagnesium chloride alone (Et$_2$O, r.t.) or in the presence of catalytic amounts of cuprous iodide[78] (Et$_2$O/THF, r.t. or 40°C) did not lead to a product, only the starting material was isolated after work-up. The inertness of epoxide 90 to the organocopper reagents may be due to steric hindrance to approach of the reagent to the reactive center (C-3).



90 R = TBDMS
91 R = H

We also attempted the epoxide opening on a synthetic intermediate without the bulky protecting group. The hydroxyepoxide **91** was obtained by epoxidation (*m*-CPBA/CH_2Cl_2) of the alcohol **88**. Its ir spectrum shows an absorption band for hydroxyl (3457 cm^{-1}). Its hrms has a fragment ion at m/z 343 corresponding to $C_{21}H_{27}O_4$ (M - $C_3H_5O_2$). The ^1H nmr spectrum of **91** displays the proton geminal to the epoxide as a doublet at δ3.31 (3.5 Hz). The other signals in the ^1H nmr spectrum of **91** are in agreement with its structure. The α orientation was assigned to the epoxide for the same reasons as given for **90**.

When the epoxide **91** was treated with lithium dimethylcuprate (Et_2O/THF, r.t.) two epimeric products were formed. The more polar epimer is **92a**. The epimer **92a** was identified as follows. Its ir spectrum shows an absorption band for hydroxyl (3440 cm^{-1}). The hrms of **92a** has a fragment ion at m/z 359 ($C_{22}H_{31}O_4$) corresponding to the molecular ion minus the dioxolane fragment ($C_3H_5O_2$). The ^1H nmr spectrum of **92a** displays a complex signal for the aromatic protons (δ7.35-7.28, 5H), a singlet for the methine of the dioxolane group (δ5.23), a one proton doublet for H-12 (δ5.27, 6 Hz), a singlet for the angular methyl (δ0.86), two doublets for hydroxyl (δ2.49, 2 Hz and δ1.73, 3 Hz), a complex signal assigned to the protons geminal to the hydroxyls (δ4.1-4.04, 2H), a triplet of doublets for H-5 (δ1.94, 12, 3.5 Hz), a one proton signal for H-4 (δ1.36, dt, 12, 2 Hz), and a three proton doublet for a methyl (δ1.3, 7 Hz). Decoupling experiments gave the following results. Irradiation of the methyl doublet at δ1.30 modified the complex signal at δ4.1-4.04. Irradiation of the signal at δ4.1-4.04 collapsed the methyl doublet at δ1.3 to a singlet and the doublet of triplets at δ1.36 (H-4) to a doublet. NOe experiments confirmed the relative stereochemical assignment at C-4 as alpha. Presaturation of the angular methyl (δ0.86) resulted in an 11% enhancement in the signal at δ1.36. All these data are consistent with the structure assigned to 92a.



92

The less polar epimer 92b has the following properties. Its ir spectrum has an absorption band for hydroxyl (3400 cm^{-1}). Its hrms has a fragment ion at m/z 359 ($C_{22}H_{31}O_4$) for the molecular ion minus $C_3H_5O_2$. The ^1H

nmr spectrum of 92b is consistent with the assigned structure. In particular, it displays a broad singlet for H-3 (δ4.39), a triplet of doublets for H-18 (δ4.08, 6.5, 2.5 Hz), two doublets for hydroxyl (δ2.6, 6.5 Hz and δ2.53, 1.5 Hz), a triplet of doublets for H-5 (δ2.01, 12, 3.5 Hz), and a three proton doublet for a methyl (δ1.31, 6.5 Hz).

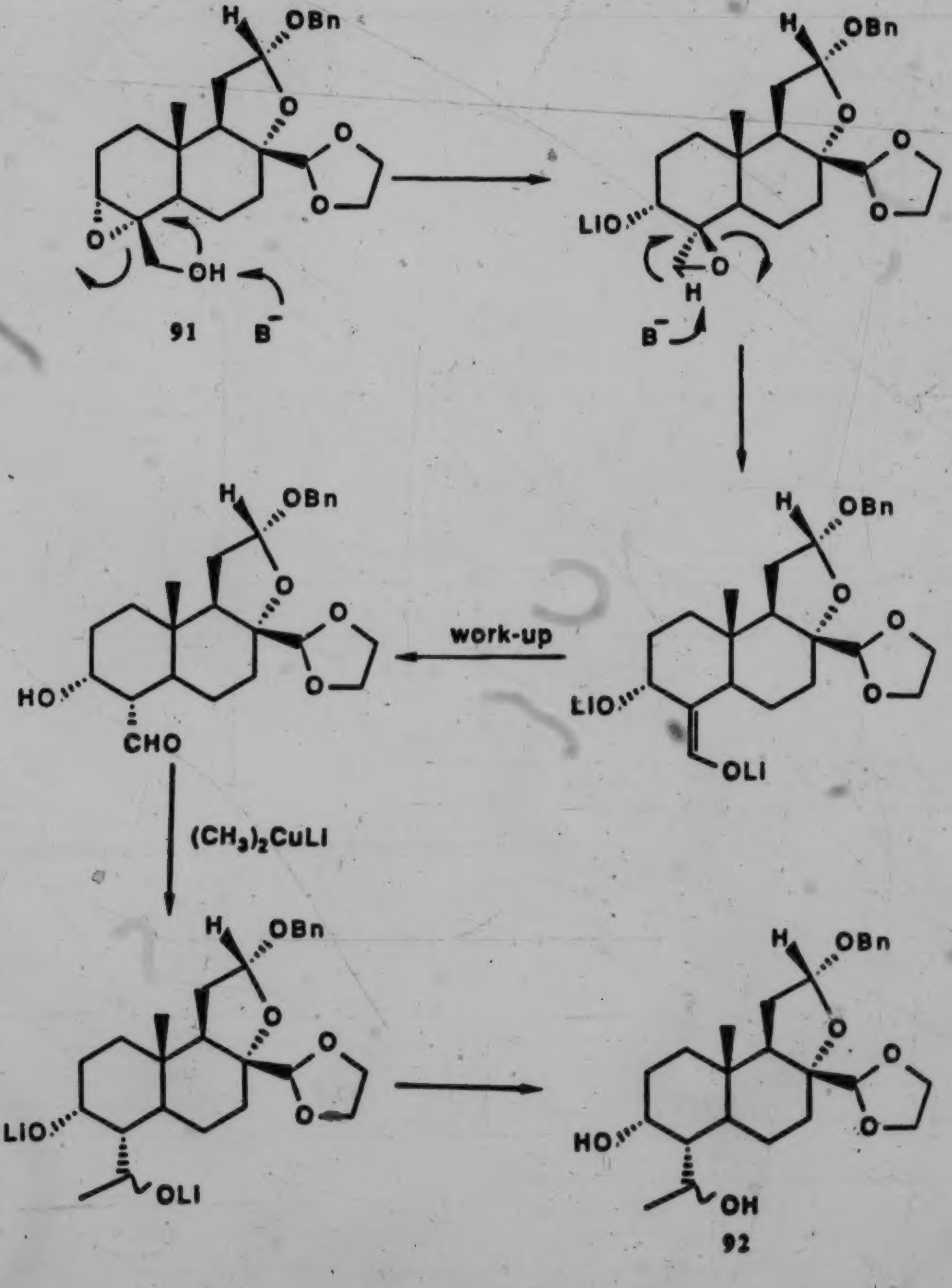
The spectroscopic data of 92a and 92b indicate that they are epimers. Because H-5 of both epimers shows a large coupling constant (12 Hz) with H-4 they must be epimeric at C-18. The proposed mechanism for the formation of 92 is shown in Scheme VII.

The first step is formation of the spiroepoxide[71] followed by opening of the epoxide to give the C-18 enolate.[72] Protonation of the enolate to the aldehyde and addition of methyllithium may have occurred during reaction work-up.

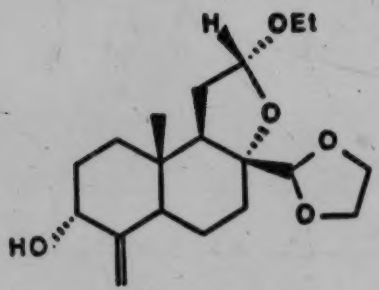
After these attempts to open the epoxide with organocopper reagents failed to introduce a β-methyl group selectively, we decided to introduce the group by a different approach. When the isomeric mixture of olefins 84 was treated with selenium dioxide in ethanol under reflux the allylic alcohol 93 was isolated in 36% yield. Its ir spectrum shows an absorption band for hydroxyl (3453 cm^{-1}) and for exocyclic olefin (1655 cm^{-1}). Its

SCHEME VII

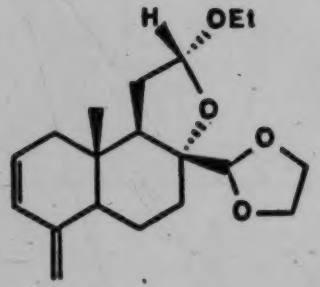
Formation of 92 from 91


H
OBn
O
O
O
OH
91
B⁻
LiO
H
B⁻
work-up
HO
CHO
LiO
OLi
(CH₃)₂CuLi
LiO
OLi
HO
OH
92

hrms has a fragment ion at m/z 337 ($C_{19}H_{29}O_5$) corresponding to $M^+ - 1$. The ^{13}C nmr displays signals for nineteen carbons consistent with its molecular formula. The ^1H nmr spectrum of 93 shows a doublet assigned to H-12 (δ5.19, 5.5 Hz), two triplets for the vinyl protons (δ4.94, 1.5 Hz and δ4.60, 1.5 Hz), a one proton triplet for one proton *geminal* to the hydroxyl (δ4.27, 2.5 Hz), and an isolated spin system corresponding to an ethyl group (δ3.85-3.75, 1H, m, δ3.43, 1H, dq, 9.5, 7 Hz, and δ1.17, 3H, t, 7 Hz). Because of the acidic nature of the reaction, the benzyl group was exchanged for an ethyl group.[79] The α orientation of the hydroxyl and its stereochemistry was implied by nOe experiments on the allylic alcohol 95.



93



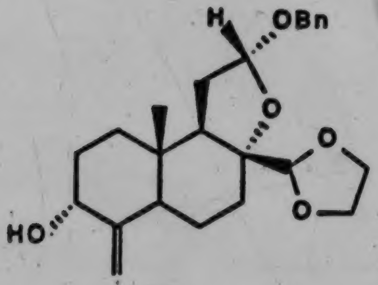
94

It was felt that a derivative of the allylic alcohol 93 might be useful in introducing the methyl group by means of an S_N2 displacement. When 93 was treated with tosylchloride (DMAP/py) only starting material was recovered after work-up. Treatment of 93 with mesyl chloride (Et_3N/CH_2Cl_2) afforded the diene 94. Its ir spectrum does not show absorption due to hydroxyl. The hrms of 94 has a fragment ion at m/z 319 ($C_{19}H_{27}O_4$) corresponding to $M^+ - 1$. The ^1H nmr spectrum of 94 is in agreement with the structure for 94, in particular, it displays four vinylic protons at δ6.2 (dd, 10, 2.5 Hz), δ5.61 (m), δ4.83 (br s), and 4.75 (br s). The ease of formation of 94 discouraged us from further attempts to use a derivative of 93 to introduce the β-methyl group.

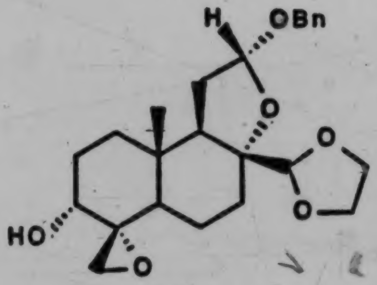
The next approach to the introduction of the methyl group was by means of a Wittig reaction on the C-3 ketone. The resulting exocyclic olefin would then be reduced to give the methyl group. The required ketone is available from the allylic alcohol.

When the olefins 84 were oxidized with SeO_2 using the method developed by Sharpless and Umbreit (t-BuOOH/CH_2Cl_2)[80] the alcohol 95 was obtained in 47% yield. Its hrms has a fragment ion at m/z 327 ($C_{21}H_{27}O_3$) corresponding to the molecular ion minus $C_3H_5O_2$. The ^1H nmr spectrum of 95 is consistent with its structure, in particular, it shows a triplet for the proton geminal to the hydroxyl (δ4.27, 2.5 Hz), and two signals for the vinyl protons (δ4.93, br s, and δ4.6, t, 1.5 Hz). NOe experiments confirmed the α orientation of the hydroxyl.

Presaturation of the broad singlet at δ4.93 resulted in a 12% enhancement of the signal at δ4.27 (H-3).



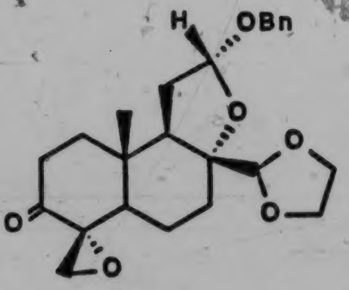
95



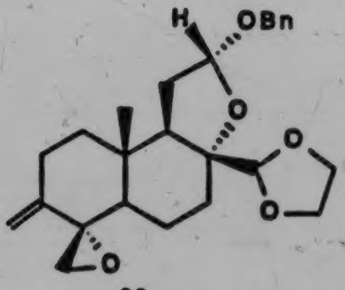
96

At this point in the synthesis, the exocyclic olefin at C-4 had been used to activate C-3. Because we planned to use catalytic hydrogenation and ozonolysis to effect transformations in other parts of the molecule, we decided to protect the olefin as its corresponding epoxide. An epoxide protecting group was chosen because of its relative stability and of the numerous methods available to transform an epoxide to an olefin.[81] Treatment of the allylic alcohol **95** with 3 eq. of m-CPBA (CH_2Cl_2, r.t.) afforded the corresponding epoxide **96**. The hrms of **96** shows a fragment ion at m/z 343 ($C_{21}H_{27}O_4$) corresponding to $M^+ - 73$ ($C_3H_5O_2$). The ^1H nmr spectrum is consistent with the assigned structure, in particular, it displays doublets at δ2.85 (4 Hz) and δ2.63 (4 Hz) corresponding to the geminal protons of the oxirane ring.

Attempts to oxidize the secondary alcohol 96 to a ketone group with PCC gave a complex mixture. The α,β-epoxyketone 97 was obtained by oxidation of 96 under the Swern conditions[82] ($(COCl)_2/DMSO/CH_2Cl_2$, -60°C followed by Et_3N, -60° → 0°C) in good yield. Its ir spectrum has a strong absorption band for carbonyl (1720 cm^{-1}). Its hrms shows a prominent peak at m/z 341 ($C_{21}H_{25}O_4$) corresponding to the molecular ion minus the dioxolane ring ($C_3H_5O_2$). The ^{13}C nmr of 97 displays signals at δ205.7 (C-3) for the carbonyl carbon, at δ60.6 (C-4) and at δ49.8 (C-18) for the carbons of the oxirane ring. The other twenty-one signals are consistent with the assigned structure.



97



98

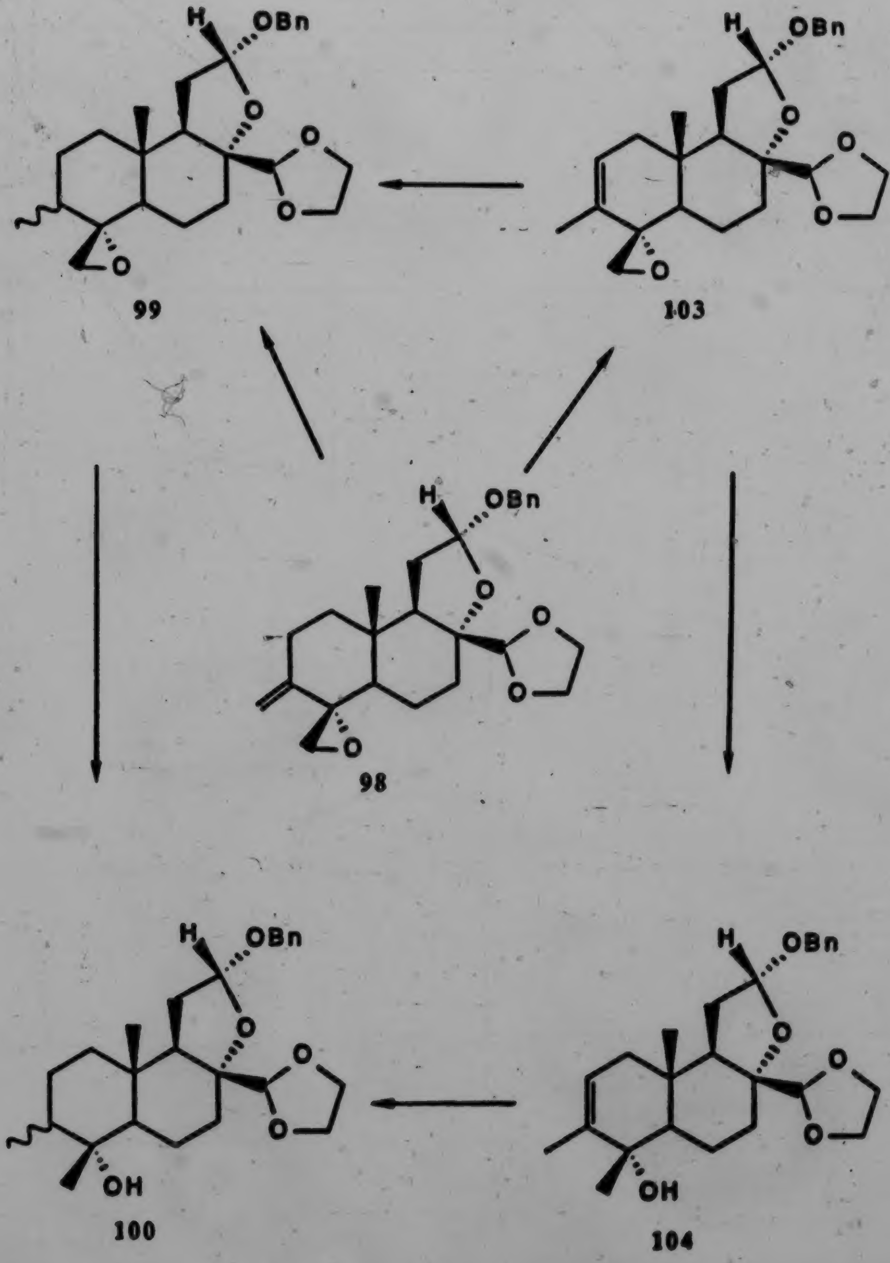
Introduction of the required carbon at C-3 was accomplished by means of the Wittig reaction on the ketone 97. When 97 was treated with the preformed ylide (Ph_3PCH_2) in DMSO (65°C)[83] no product was formed. Treatment of the ketone 97 under the conditions reported by Conia and Limasset[84] (potassium t-amoxide/triphenyl methyl phosphonium bromide/benzene) afforded the exocyclic olefin 98 in 61% yield after purification. The ir spectrum of 98 shows an absorption band at 1645 cm^{-1} characteristic of the exocyclic methylene. Its hrms has a small fragment ion at m/z 411 ($C_{25}H_{31}O_5$) corresponding to $M^+ - 1$, and another at m/z 339 ($C_{22}H_{27}O_3$) for the molecular ion minus the characteristic loss of $C_3H_5O_2$. The ^1H nmr spectrum of 98 displays the vinyl protons as two triplets (δ4.95, 2 Hz and δ4.69, 2 Hz), and the protons of the oxirane ring as two doublets (δ2.85, 5.5 Hz and δ2.46, 5.5 Hz). The other signals in the ^1H nmr spectrum of 98 are in agreement with its structure.

The β-methyl group at C-3 present in our target molecule should be obtained by reduction of the olefin of 98. We felt that the desired β stereochemistry of the C-3 methyl could be obtained by the use of the appropriate reaction conditions. Scheme VIII summarizes the different transformations used in an attempt to convert compound 98 into a compound with the C-3 β-methyl group, compound 100-β. The results obtained in these steps are discussed below.

Catalytic hydrogenation of 98 using platinum oxide in ethanol under atmospheric pressure afforded the epimeric mixture 99. The ratio of the α:β C-3 methyl groups was ca. 4:1 respectively. This ratio was determined by

SCHEME VIII

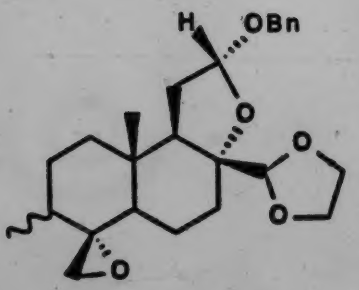
Intermediates in the conversion of 98 to 100


H
OBn
O
O
O
99
103
98
100
104
OH

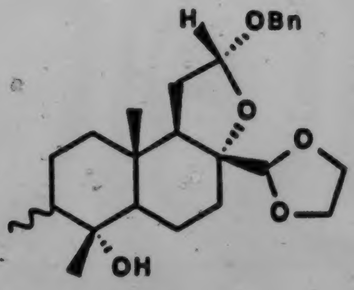
measuring the integration of the signals corresponding to the protons of the epoxide. The assignment of the α orientation to the major epimer in the mixture was based on correlation with a compound obtained in a later step. The hrms of **99** displays a fragment ion at m/z 341 ($C_{22}H_{29}O_3$) corresponding to the molecular ion minus $C_3H_5O_2$. The ^1H nmr spectrum of **99** displays the following signals for the major component (α epimer); two doublets for the protons in the oxirane ring (δ2.75, 4.5 Hz and δ2.53, 4.5 Hz), a doublet for the C-3 CH_3 (δ1.1, 7 Hz), and a singlet for the angular methyl (δ0.87). The minor component (β epimer) shows the following signals in the ^1H nmr spectrum of **99**; two doublets for the protons in the oxirane ring (δ2.69, 4 Hz and δ2.57, 4 Hz), a singlet for the angular methyl (δ0.83), and a doublet for the C-3 CH_3 (δ0.72, 6.5 Hz). Other signals in the ^1H nmr spectrum of **99** are consistent with the structures.

Catalytic hydrogenation of **98** using PtO_2 in Et_2O, cyclohexane or 10% palladium on activated carbon in cyclohexane gave an epimeric mixture **99** in a similar ratio. When 5% Rh/C in cyclohexane was used in the hydrogenation of **98**, the ratio of the epimers of **99** was ca. 1.7:1 with the α epimer as the major component.

The stereochemistry of the major component of the epimeric mixture **99** was determined as follows. The epoxide ring in 99 was opened with superhydride ($LiEt_3BH$/THF) to give alcohol 100 as an epimeric mixture. The ^1H nmr spectrum of 100 displays two singlets for the C-4 CH_3 (δ1.17, 2.4H and δ0.95, 0.6H), two doublets for the C-3 CH_3 (δ1.01, 7 Hz, 2.4H and δ0.91, 7 Hz, 0.6H), and two singlets for the angular methyl (δ0.89, 2.4H and δ0.84, 0.6H). The major component of the mixture, compound 100-α, was separated by crystallization. Its ir spectrum shows an absorption band for hydroxyl (3530 cm^{-1}). Its hrms has a fragment ion at m/z 343 ($C_{22}H_{31}O_3$) corresponding to the molecular formula

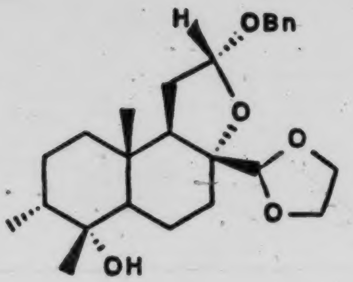


99

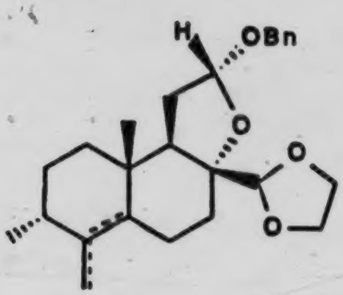


100

($C_{25}H_{36}O_5$) minus 73 ($C_3H_5O_2$). The ^1H nmr spectrum of 100-α displays two methyl singlets (δ1.17, C-4 CH_3 and δ0.89, C-10 CH_3), a methyl doublet (δ1.01, 7 Hz, C-3 CH_3), a one proton doublet (δ5.26, 6 Hz) assigned to H-12, a five proton multiplet (δ7.35-7.23) corresponding to the aromatic protons, and a one proton singlet (δ5.20) for H-14.



100-α

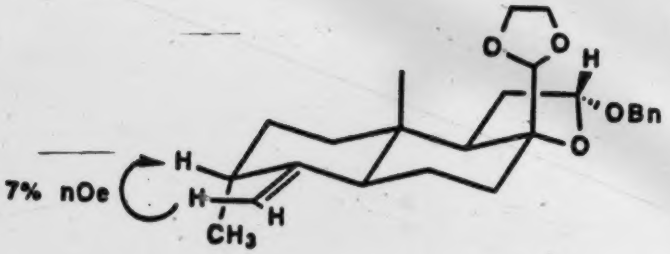


101

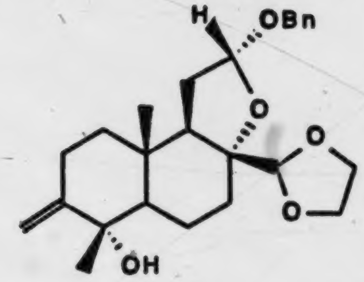
Treatment of 100-α with p-toluenesulfonyl isocyanate (toluene, forms the corresponding carbamate) followed by pyrolysis (refluxing toluene)^{85} afforded an isomeric mixture of olefins, compound 101. Analysis of the ^{1}H nmr spectra of 101 indicates that the olefinic isomers are in a ratio of 7:3. Because each of the olefins has a doublet corresponding to the C-3 CH_3 (δ1.08 and δ0.99), the isomers were identified as the $\Delta^{4,5}$ and $\Delta^{4,(18)}$ olefins. The exocyclic olefin is the major component of the mixture (^{1}H nmr).

Decoupling experiments confirm the chemical shift assigned to H-3. Irradiation of the doublet at δ1.08 (C-3 CH_3) collapsed the multiplet at δ2.53 (H-3) to a doublet. The relative stereochemistry at C-3 was confirmed by nOe experiments. Presaturation of the broad singlet at δ4.73 (vinyl H) gave a 7% enhancement at δ2.53 (H-3). The observed enhancement in the nOe experiments indicate a close proximity between H-3 and the vinyl proton, thus the α orientation was assigned to the C-3 CH_3 (see Figure 4). The relative stereochemistry at C-3 of muzigadial (2), as determined by nOe experiments,[3a] was shown to be β. Unfortunately compound 101 and the major component of its epoxide precursor 99 have the opposite stereochemistry at C-3.

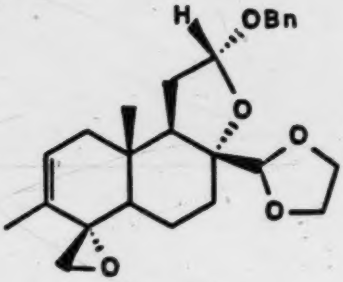
Figure 4. Conformation of 100-α.



The results obtained in the catalytic hydrogenation of 98 indicate that the β face of the olefin is the more accessible face, as observed by others for catalytic hydrogenation of 4-t-butylmethylenecyclohexane.[86] We felt that opening the epoxide of 98 to give an axial methyl group at C-4 might favor formation of the desired β product during the reduction. Treatment of 98 with superhydride ($LiEt_3BH$) afforded the allylic alcohol 102 in good yield. NOe experiments on the C-4 methyl confirmed the assigned stereochemistry at C-4. Presaturation of the signal at δ1.17 (C-4 CH_3) gave a 16% enhancement for the signal of the angular methyl group (δ0.97). These experiments also confirm the earlier assumption that in epoxide formation with peracid, the peracids would approach the exocyclic olefin of 95 from the α face to give 96.



102



103

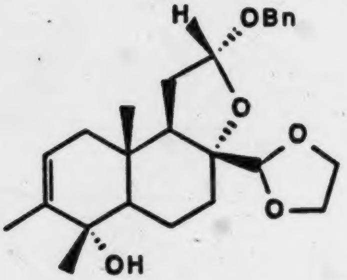
Catalytic hydrogenation of 102 with PtO_2 in ethanol or 5% Rh/C in cyclohexane (1 atm) afforded 100 as a mixture of α and β epimers in a ratio ca. 2:1 respectively (determined by ^1H nmr). Unfortunately the presence of the C-4 β-methyl group in 102 did not create enough of a steric effect to cause a substantial change in the stereochemistry of the reduction.

The use of 10% Pd/C in the catalytic hydrogenation (1 atm) of olefin 98 gave better results. The use of solvents such as ethyl ether, isopropyl ether, benzene, or acetonitrile provided the isomeric mixture, compound 99, in which the β epimer (δ2.69, 4 Hz and δ2.57, 4 Hz) is the major component (α:β ratio, 1:2; determined by ^{1}H nmr). The ^{1}H nmr spectrum of the crude product also shows signals for impurities. The use of ethanol or ethyl acetate afforded complex mixtures.

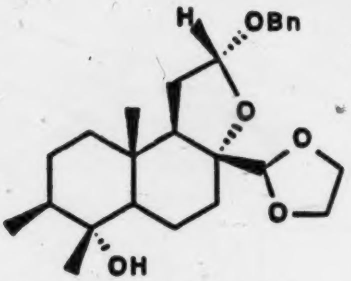
When the olefin 98 was treated with Pd/C and H_2 (1 atm) in THF or acetonitrile for a short period of time (*ca.* 1 h) compound 103 was formed as the major component. The product contained a small amount of compound 99. The ^{1}H nmr spectrum of 103 displays a one proton multiplet assigned to the vinyl proton (δ5.61) and a broad doublet for the vinyl methyl (δ1.47, 1 Hz).

It is known that olefin isomerization is in competition with reduction of an olefin when palladium is used as the catalyst.[87] The ease of isomerization of 98 to 103 may explain why the catalytic hydrogenation of 98 with palladium gives the β epimer as the major product. Addition of hydrogen to the endocyclic olefin from the α face forms the β epimer at C-3 as the major product.

Treatment of epoxide **103** with PtO_2 (EtOH or EtOAc) or 10% Pd/C (THF or cyclohexane) under catalytic hydrogenation conditions (H_2, 1 atm) provided complex mixtures. Ring opening of the epoxide of **103** with superhydride ($LiEt_3BH$) afforded the allylic alcohol **104**. Its ir spectrum has an absorption band for hydroxyl (3400 cm^{-1}). The ^1H nmr spectrum of **104** displays a broad doublet for a vinyl proton (δ5.33, 6 Hz), a singlet for hydroxyl (δ1.06), and a signal assigned to the vinyl methyl (δ1.74, br d, 1.5 Hz).



104



100-β

Treatment of **104** with PtO_2 or 10% Pd/C in ether under hydrogen (1 atm) did not lead to reaction. When **104** was treated with 10% Pd/C in ethyl ether under pressure (H_2, 3 atm) the hydrogenated alcohol **100** (epimeric mixture at C-3) was obtained. Analysis of the ^1H nmr spectrum of **100** shows the α and β epimers at C-3 in a ratio of 1:8, respectively. The ^{1}H nmr spectrum of the major isomer, **100-β**, is consistent with the assigned structure, in particular, it displays a three proton singlet for the C-4 CH_3 (δ0.93), a doublet assigned to the C-3 CH_3 (δ0.90, 7 Hz), and a singlet for the angular methyl (δ0.84).

With the formation of **100-β**, the synthetic route for the introduction of the β-methyl group at C-3 has been established. The conversion of **100-β** to muzigadial (**2**) employing the sequence of reactions described for warburganal (**1**), is currently underway in our laboratories.

CONCLUSIONS

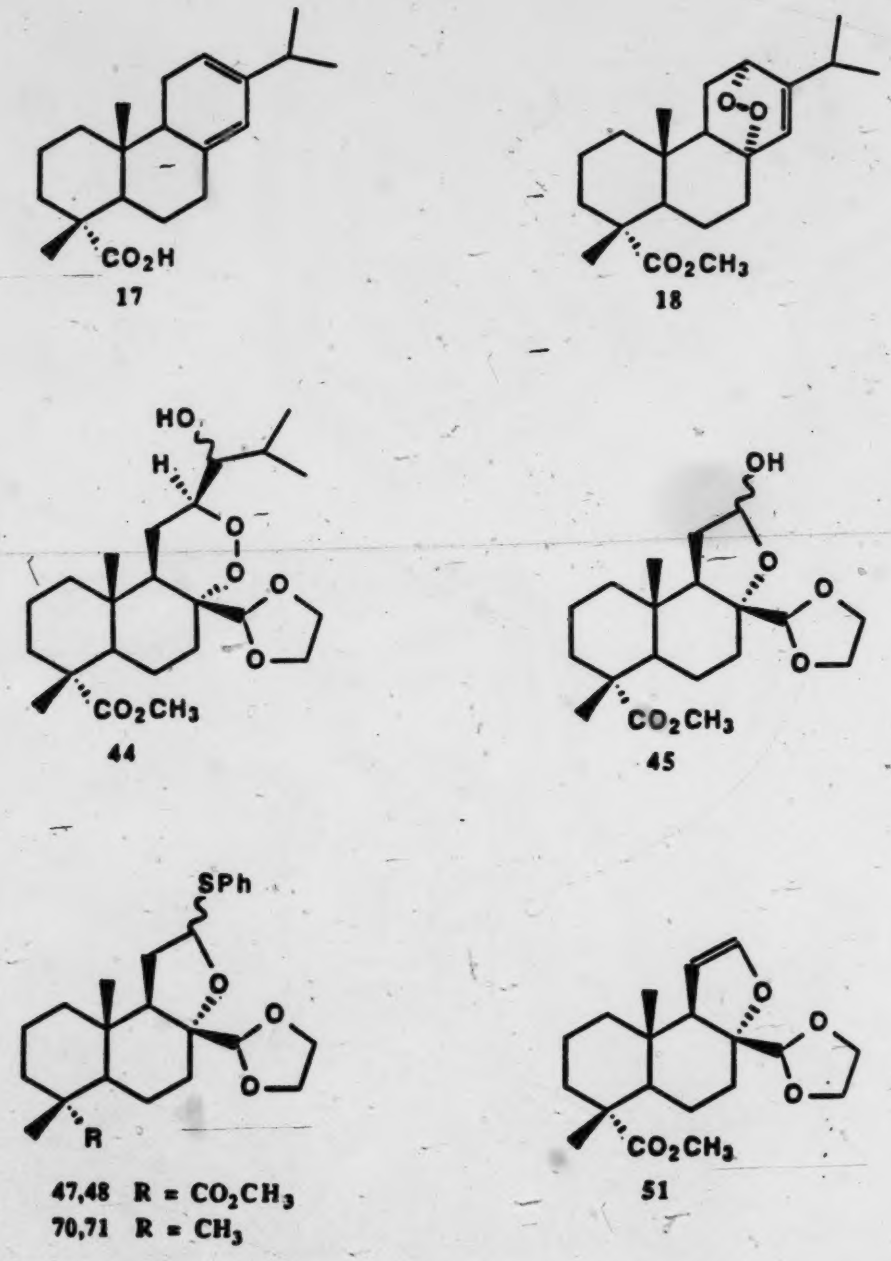
In summary, we describe in this thesis the transformation of levopimaric acid (**17**) to warburganal (**1**) (Scheme IX) and to compound **100-β**, a potential intermediate for the synthesis of muzigadial (**2**).

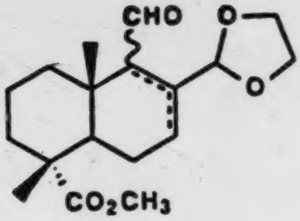
These transformations were carried out as follows. Levopimaric acid (**17**) was converted to the endoperoxide **18**. Ozonolysis of the double bond followed by protection of the aldehyde and reduction of the ketone provided the hydroxyperoxide **44**. The key intermediate **45** was formed by heterolytic fragmentation of **44** under basic conditions. Compound **45** was transformed to the enol ether **51** *via* the corresponding hemithioacetals **47**, **48**. The enol ether **51** was converted to the isomeric mixture of olefins (**52**, **53**, **58**). The olefins were hydroxylated at C-9 and the protecting group at C-8 was removed to give 4α-methoxycarbonylwarburganal (**20**).

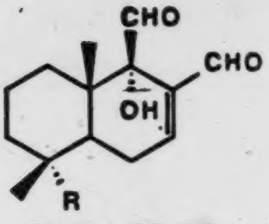
With the formation of **20** we established a practical route to remove the top "isoprene unit" of levopimaric acid (**17**) and to introduce the functionalities present in ring B of warburganal. The remaining transformation required to complete the synthesis of warburganal (**1**) was the reduction of the carboxylate group to a methyl

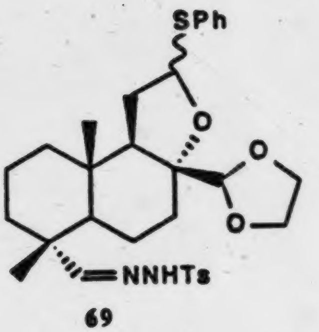
SCHEME IX

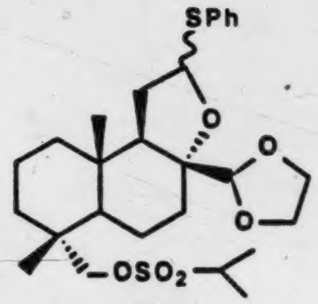
Synthesis of warburganal


CO₂H
17
O–O
CO₂CH₃
18
HO
H
O
O
O
O
CO₂CH₃
44
OH
O
O
O
CO₂CH₃
45
SPh
O
O
O
R
47,48 R = CO₂CH₃
70,71 R = CH₃
O
O
O
CO₂CH₃
51


52,53,58


20 R = CO_2CH_3
1 R = CH_3


69


74,75

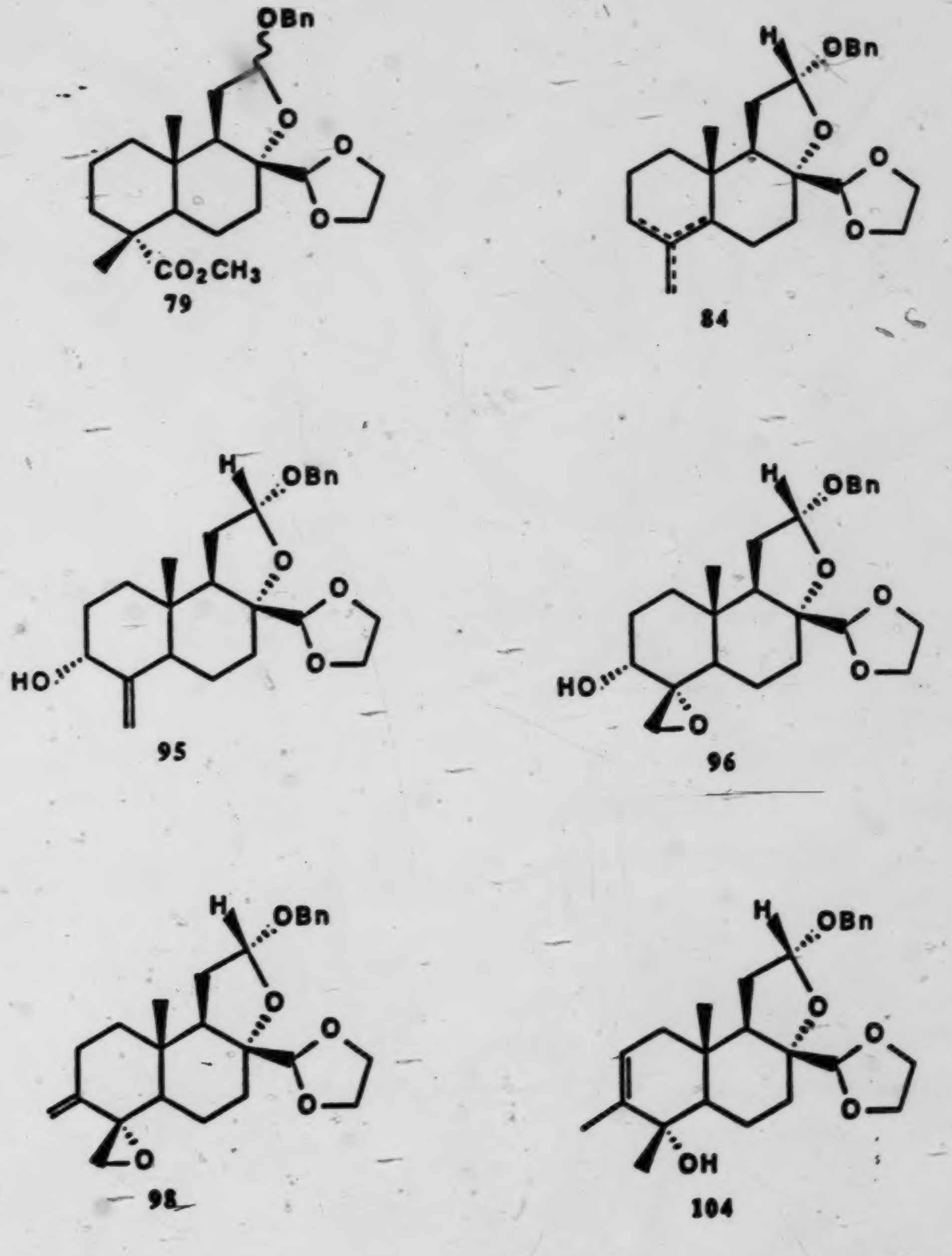
group. It was accomplished in two different ways. The epimeric mixture of hemithioacetals 47, 48 was converted either to the tosylhydrazone 69 or to the epimeric mixture of isopropylsulfonates (74,75). The hydrazone 69 was reduced with a disubstituted borane to the gem-dimethylhemithioacetals 70, 71 while the sulfonate of 74, 75 was displaced with hydride to provide 70, 71. Both of these methods brought about reduction at the neopentyl carbon. With compounds 70, 71 in hand, the synthesis of warburganal (1) was completed using the route described above for the synthesis of 4α-methoxycarbonylwarburganal (20) (Scheme IX).

In the synthesis directed to muzigadial (2) we used the hemiacetals 45 in its protected form (79) to modify ring A (Scheme X). Conversion of the carboxylate group of 79 to the corresponding tertiary alcohol followed by fragmentation provided an isomeric mixture of olefins 84 (the desired exocyclic olefin was the major component). This sequence of reactions proved to be the least cumbersome and most stereoselective of the reactions attempted for the formation of the exocyclic methylene.

Activation of C-3 was effected by allylic oxidation of 84 to provide the secondary alcohol 95. The olefin in C-4 was protected as its corresponding epoxide 96. Epoxyalcohol 96 was oxidized to the ketone and this was

SCHEME X

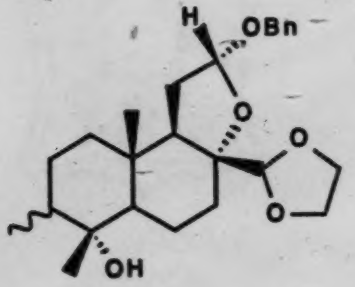
Towards the synthesis of muzigadial


OBn
CO2CH3
79
H
OBn
84
H
OBn
HO
95
H
OBn
HO
96
H
OBn
98
H
OBn
OH
104

converted to the olefin **98** by means of a Wittig reaction. At this point we had attached the one carbon unit at C-3 and there remained the stereoselective reduction of the olefin from the alpha face to obtain the correct stereochemistry at C-3.

The terminal methylene in **98** was isomerized to the endocyclic olefin, the epoxide was opened to give the corresponding tertiary alcohol **104**, and this was reduced under catalytic hydrogenation conditions to the epimeric mixture of the alcohols **100**. The C-3 β-epimer was the predominant product.

We have thus synthesized an intermediate with a β-methyl group at C-3 and a masked exocyclic olefin at C-4. The conversion of this intermediate to muzigadial (**2**) employing the sequence of reactions previously described for our successful synthesis of warburganal is currently under investigation in our laboratories.



100

EXPERIMENTAL

Unless otherwise stated the following particulars apply. All reactions were run under a positive pressure of an inert gas. Reactions requiring anhydrous conditions were performed in oven-dried glassware (115°C, 2 h), cooled in a dessicator, assembled, and sealed with a rubber septa (when applicable) and purged with an inert gas. The term in vacuo refers to solvent removal via Buchi rotoevaporator at water aspirator pressure. Solvents were distilled before use for chromatography or extraction. Anhydrous solvents were distilled from appropriate drying agents: diethyl ether (Et_2O) by distillation from a blue solution of sodium benzophenone ketyl, tetrahydrofuran (THF) by distillation from a blue solution of potassium benzophenone ketyl, dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), toluene, pyridine (py), triethylamine (Et_3N), diisopropylamine, diisopropylethylamine, benzyl alcohol, oxalyl chloride, dimethylsulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPA) by distillation from calcium hydride (the latter three under reduced pressure and stored over molecular sieves (3Å) under nitrogen); Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62-70°C; the commercial solutions (Aldrich) of methyllithium in ether, n-butyllithium in THF and phenyllithium in ether were titrated before use by the diphenylacetic acid method;[88] oxodiperoxymolybdenum(pyridine)-hexamethylphosphoramide (Aldrich) was used as received.

Flash column chromatography was performed by using E. Merck silica gel 60 (230-400 ASTM mesh) according to the procedure of Still.[89] Analytical thin layer chromatography (tlc) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For tlc the visualization of the chromatograms was completed by spraying with a solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5% w/v) in sulfuric acid (3%, v/v), followed by careful charring on a hot plate.

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. Fourier transform infrared spectra were recorded on a Nicolet 7199 FT interferometer. Ultraviolet spectra were recorded on a Hewlett Packard HP8450A diode array spectrometer coupled to a 7470A plotter.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on Bruker WP-80 (at 80 MHz), Varian HA-100 (at 100 MHz), Bruker WH-200 (at 200 MHz), Bruker WM-360 (at 360 MHz), Bruker WH-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard and measurements are reported in ppm downfield from TMS (δ). ^{13}C nuclear magnetic resonance (^{13}C nmr) spectra were measured on a Bruker WH-200 (at 50.3 MHz) or Bruker WH-400 (100.6 MHz) spectrometers. For ^{13}C nmr, deuterochloroform ($CDCl_3$) was employed as the internal standard (assigned as 77.0 ppm downfield from TMS) and measurements are reported in ppm downfield from TMS (δ).

Carbon-13 multiplicities were derived from gate decoupling spin echo experiments.[90] Nuclear Overhauser enhancements (nOe) were determined by making all the data points of the control (undecoupled) spectrum negative and computer-adding it to the free induction decay (FID) of the decoupled spectrum before Fourier transformation. Positive enhancements are defined as multiplets possessing an antiphase with respect to the decoupled signal. Samples for nOe measurements were deoxygenated with nitrogen or argon for 10 min prior to use. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; δ, chemical shift.

High resolution electron impact mass spectra (hrms) were recorded on an A.E.I. MS-50 mass spectrometer coupled to a DS50 computer. Chemical ionization* mass spectra (cims) and low resolution electron impact mass spectra (lrms) were obtained using an A.E.I. MS-9 mass spectrometer. Data are reported as m/z (relative intensity). Unless diagnostically significant, peaks with intensities less than 20% of the base peak are omitted. Optical rotations were determined on a Perkin Elmer model 141 polarimeter with a sodium lamp (589 nm) at room temperature. Combustion elemental analyses were performed by the Microanalytical Laboratory of the University of Alberta.

Levopimaric acid **17**

Levopimaric acid (**17**) was isolated from pine oleoresin (Naval Stores and Timber Production Laboratory. Olustee, Florida, U.S.A.) using the procedure described;[18] m.p. 128°C; tlc: R_f 0.23 (cyclohexane/ethyl acetate, 70:30); $[\alpha]_D$ -265 (c 6.6, MeOH); ir ($CHCl_3$, cast): 3600-2360, 1694, 1283, 763 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$):

---

*Ammonia as reagent gas.

δ5.51 (1H, bs, H-12), 5.12 (1H, bt, 3.5 Hz, H-14), 2.40-2.02 (6H, m), 1.93 (1H, dd, 12, 3 Hz, H-5α), 1.86-0.88 (8H, m), 1.16 (3H, s, C-4 CH_3), 0.96 (6H, d, 7 Hz, CH_3-16,17), 0.89 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ185.4, 138.9, 138.5, 119.1, 114.8, 49.5, 49.2, 47.5, 40.2, 37.1, 36.7, 35.8, 33.2, 33.2, 26.3, 22.5, 21.3, 21.2, 17.9, 16.2, 14.1; hrms: m/z calcd for $C_{20}H_{30}O_2$ (M^+): 302.2238, found: 302.2246(76), 187(29), 146(76), 134(50), 123(19), 121(19), 117(23), 105(42), 91(100).

Methyl levopimarate 25

An etheral solution of diazomethane was added dropwise with stirring to a solution of levopimaric acid (5.092 mg, 16.8 mmol) in ether (200 mL) at 0°C until the yellow color indicating excess diazomethane remained. The reaction mixture was dried (Na_2SO_4), and concentrated *in vacuo* to give 25 as a solid (5.230 g, 98%). m.p. 60-62°C; tlc: R_f 0.76 (cyclohexane/ethyl acetate, 70:30); 0.52 (Skellysolve B/ethyl acetate, 85:15); ir (CH_2Cl_2, cast): 1728, 1382, 1245, 1192, 1170, 1120 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ5.5 (1H, d, 1.5 Hz, H-14), 5.11 (1H, t, 4 Hz, H-12), 3.65 (3H, s, C-18 OCH_3), 2.38-2.0 (5H, m), 1.91 (1H, dd, 12.75, 2.75 Hz, H-5), 1.84-1.38 (9H, m), 1.17 (3H, s, C-4 CH_3), 0.95 (6H, d, 7 Hz, CH_3-16,17), 0.89 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{21}H_{32}O_2$ (M^+):

316.2394, found: 316.2402(91), 299(9), 257(9), 239(34), 187(19), 181(21), 146(69), 133(41), 123(29), 117(23), 105(36), 101(40), 91(100).

Methyl 8α,12α-epidioxy-abiet-13-enate **18**

A solution of the methyl ester **25** (4.040 g, 12.7 mmole) and rose bengal (50 mg) in 95% ethanol (240 mL) was irradiated with a 40 watt Luminate® lamp while oxygen bubbled through the solution. After 9 h the solvent was removed *in vacuo*. The residue was dissolved in ether (300 mL), washed with saturated $NaHCO_3$ (3×), water (2×), brine (2×), dried (Na_2SO_4), and concentrated to give a pink solid (4.350 g). Purification by flash chromatography over silica gel eluting with Skellysolve B/ethyl acetate, 85:15 gave the endoperoxide **18** as a solid (3.360 g, 76%). An analytical sample of the endoperoxide was obtained by recrystallization from Skellysolve B. m.p. 102°C; tlc: R_f 0.4 (Skellysolve B/ethyl acetate, 80:20), 0.41 (dichloromethane/ethyl acetate, 95:5); $[\alpha]_D$ +82.6 (*c* 1.4, $CHCl_3$); ir ($CHCl_3$, cast): 1715, 1645, 890 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ5.88 (1H, t, 1.5 Hz, H-14); 4.63 (1H, dt, 4.5, 1.5 Hz, H-12), 3.69 (3H, s), 2.51 (1H, quintet d, 7, 1.5 Hz, H-15), 2.25 (1H, ddd, 14, 9.5, 4.5 Hz, H-11α), 1.98 (1H, dd, 9, 5.5 Hz, H-9), 1.94-1.02 (12H, m), 1.14 (3H, s, C-4 CH_3), 1.12 (3H, d, 7 Hz, CH_3-16), 1.08 (3H, d, 7 Hz, CH_3-17), 0.57 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ178.8 (s, C-18), 149.1 (s, C-13), 124.7 (d, C-14), 76.9 (s, C-8), 74.7 (d, C-12), 51.9 (q, C-18 OCH_3), 50.2 (d), 49.3 (d), 47.1 (s, C-4), 36.9 (t), 36.8 (t), 36.3 (s), 32.2 (t), 31.1 (d, C-15), 25.1 (t), 21.7 (t), 20.4 (q, C-16), 20.2 (q, C-17), 17.1 (t), 16.6 (q), 15.2 (q); hrms: m/z calcd for $C_{21}H_{32}O_4$ (M^+): 348.2292; found: 348.2300(5), 316(67), 305(7), 278(7), 259(10), 217(16), 173(17), 146(34), 121(100), 105(30); Analysis: calcd for $C_{21}H_{32}O_4$: C 72.38, H 9.25; found: C 72.55, H 9.35.

Methyl dehydroabietate **26** was also separated by flash chromatography as an oil (230 mg, 6%). tlc: R_f 0.53 (Skellysolve B/ethyl acetate, 8:2), 0.68 (dichloromethane/ethyl acetate, 95:5); ir (CH_2Cl_2, cast): 1728, 1246, 821 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ7.13 (1H, d, 8 Hz, H-11), 6.96 (1H, dd, 8, 2 Hz, H-12), 6.85 (1H, bs, H-14), 3.64 (3H, s, C-18 OCH_3), 2.93-2.83 (3H, m), 2.29 (1H, bd, 12 Hz), 2.23 (1H, dd, 12.5, 2 Hz, H-5), 1.9-1.2 (7H, m), 1.24 (6H, d, 7 Hz, CH_3-16,17), 1.19 (6H, s, C-4 and 10 CH_3); hrms: m/z calcd for $C_{21}H_{30}O_2$ (M^+): 314.2238; found: 314.2245(25), 299(26), 239(100), 197(7), 141(9), 129(9), 117(6).

(1S,5R,6R,9R,12S,14R)-1,5-Dimethyl-10,11-dioxa-12-isopropylcarbonyl-9-formyl-5-methoxycarbonyltricyclo-$[8,4,0,0^{9,14}]$tetradecane **27**

A solution of the endoperoxide **18** (820 mg, 2.3 mmol) in dichloromethane-methanol (9:1, 100 mL) was cooled in a dry ice-acetone bath. Ozone was bubbled through the solution until the solution remained pale blue. Excess ozone was removed with N_2, then methyl sulfide (0.4 mL) was added to the solution. The reaction mixture was allowed to reach room temperature and the solvent evaporated. The residue was dissolved in Et_2O, washed with water (2×), brine (×), dried (Na_2SO_4), and the solvent removed to give the ketoaldehyde **27** as an oil (860 mg, 98%). An analytical sample was obtained by flash chromatography (CH_2Cl_2/EtOAc, 98:2). tlc: R_f 0.67 (chloroform/ethyl acetate, 90:10), 0.55 (dichloromethane/ethyl acetate, 95:5); $[\alpha]_D$ -183.5 (c 0.2, $CHCl_3$); ir ($CHCl_3$, cast): 2750, 1723 (br,vs), 1248 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ9.77 (1H, s), 4.85 (1H, dd, 9, 4.5 Hz, H-12), 3.67 (3H, s), 2.85 (1H, quintet, 7 Hz, H-15), 2.13-1.21 (14H, m), 1.17 (3H, s, C-4 CH_3), 1.14 (3H, d, 7 Hz, CH_3-16), 1.07 (3H, d, 6.5 Hz, CH_3-17), 0.95 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{21}H_{32}O_6$ (M^+): 380.2190; found: 380.2199 (0.3), 352(13), 281(16), 264(16), 263(22), 203(10), 121(34), 71(100). Analysis:

calcd for $C_{21}H_{32}O_6$: C 66.33, H 8.48; found: C 66.35, H 8.59.

(1S,5R,6R,9R,12S,14R)-1,5-Dimethyl-9-(1,1-dimethoxymethyl)-10,11-dioxa-12-isopropylcarbonyl-5-methoxycarbonyltricyclo[8,4,0,$0^{9,14}$]tetradecane **28**

A solution of the ketoaldehyde **27** (860 mg, 2.26 mmol) and p-toluenesulfonic acid (cat. amount) in trimethylorthoformate (10 mL) was stirred at room temperature for 20 h. The solution was diluted with Et_2O, washed with saturated $NaHCO_3$ (2×), H_2O (×), brine (2×), dried (Na_2SO_4), and evaporated in vacuo to give **28** as a solid (930 mg). The crude product was recrystallized from Et_2O to yield colorless needles (665 mg, 69%). m.p. 167-8°C; tlc: R_f 0.38 (Skellysolve B/ethyl acetate, 60:40); 0.65 (ethyl ether/benzene, 60:40); $[\alpha]_D$ -119 (c 0.75, $CHCl_3$); ir ($CHCl_3$, cast): 1722, 1248, 1128, 1068 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ4.72 (1H, dd, 11, 3 Hz, H-12), 4.64 (1H, s, H-14), 3.67 (3H, s, C-18 OCH_3), 3.60 (3H, s, C-14 OCH_3), 3.46 (3H, s, C-14 OCH_3), 2.96 (1H, quintet, 7 Hz, H-15), 2.20-0.95 (14H, m), 1.17 (3H, s, C-4 CH_3), 1.10 (3H, d, 7 Hz, C-16), 1.08 (3H, d, 7 Hz, CH_3-17), 0.91 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{19}H_{31}O_6$ (M^+ - C_4H_7O): 355.2112, found: 355.2121(0.3), 263(1.6), 121(3), 81(2), 75(100); cims (NH_3): 444 (M^+ + 18,100);

Analysis: calcd for $C_{23}H_{38}O_7$: C 64.76, H 8.98, found: C 64.95, H 9.08.

(1S,2R,3R,6R,7R)-1,7-Dimethyl-3-(1,1-dimethoxymethyl)-2-(2,3-dioxo-4-methylpentyl)-3-hydroxy-7-methoxycarbonylbicyclo[4,4,0]decane **29**

A solution of the peroxide **28** (107.1 mg, 0.25 mmol) and triethylamine (0.04 mL, 0.28 mmol) in chloroform (5 mL) was stirred for 48 h at room temperature. The resulting yellow solution was concentrated *in vacuo* to give **29** as an oil. The crude product was purified by flash column chromatography (Skellysolve B/acetone, 3:1) to give pure α-diketone **29** (103 mg, 96%). tlc: R_f 0.33 (Skellysolve B/acetone, 3:1), 0.33 (Skellysolve B/ethyl acetate, 60:40); ir ($CHCl_3$, cast): 3456 (br), 1725, 1245, 1119, 1070 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ4.79 (s), 4.64 (s), 4.54 (s), 4.36 (s), 4.01 (s), are in a ratio of 3:3:1:1:1. All the other signals are repeated; cims: 444(M^+ + 18,19), 426 (M^+, 10), 412(100).

(1S,5R,6R,9R,13R)-1,5-Dimethyl-9-(1,1-dimethoxymethyl)-11-isopropylcarbonyl-11-methoxy-5-methoxycarbonyl-10-oxatricyclo[7,4,0,$0^{9,13}$]tridecane **30**

α-Diketone **29** (199.4 mg, 0.47 mmol), *d,l*-camphorsulfonic acid (cat. amount) and trimethylorthoformate (5 mL) were stirred for 12 h at room temperature. The solution was diluted with Et_2O, washed with saturated $NaHCO_3$ (3×), H_2O (×), brine (2×), dried (Na_2SO_4), and the solvent removed in vacuo to give a solid (179.5 mg). The solid was recrystallized from Skellysolve B to afford **30** as colorless needles (101.9 mg, 49%). m.p. 180-182°C; tlc: R_f 0.38 (Skellysolve B/ethyl acetate, 3:2); ir (CH_2Cl_2, cast): 1726, 1247, 1119, 1067, 1008, 955 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ4.49 (1H, s, H-14); 3.70 (3H, s, C-18 OCH_3), 3.56 (3H, s), 3.34 (1H, quintet, 7 Hz, H-15), 3.26 (3H, s), 3.25 (3H, s), 2.46 (1H, dd, 15, 12 Hz, H-11β), 2.35 (1H, dt, 12, 3 Hz, H-7β), 2.07 (1H, dd, 15, 7 Hz, H-11α), 1.90 (1H, dd, 10, 3.5 Hz, H-5), 1.83 (1H, dd, 11, 5 Hz), 1.74 (1H, dd, 12, 7 Hz, H-9), 1.7-1.01 (8H, m), 1.19 (3H, s, C-4 CH_3), 1.14 (3H, d, 7 Hz, CH_3-16), 1.09 (d, 7 Hz, CH_3-17), 0.92 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{20}H_{33}O_6$ ($M^+ - C_4H_7O$): 369.2268, found: 369.2277(37), 365(18), 337(23), 305(20), 273(27), 263(32), 245(53), 171(15), 121(15), 75(100); cims (NH_3): 458 (M^+ + 18, 43), 426(35), 409(100); Analysis: calcd for $C_{24}H_{40}O_7$: C 65.43, H 9.15, found: C 65.34, H 9.20.

(1S,5R,6R,9R,13R)-1,5-Dimethyl-9-(1,1-dimethoxymethyl)-11-(2-^{2}H)-isopropylcarbonyl-11-methoxy-5-methoxycarbonyl-10-oxatricyclo[$7,4,0,0^{9,13}$]tridecane 31

A small piece of metallic sodium was dissolved in methanol-d_1 (1 mL), then ketone **30** (8 mg, 0.018 mmol) was added to the solution. After 12 h at room temperature the reaction was quenched with 1 drop of H_2O, the solvent removed and the residue dissolved in CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield a solid (7.5 mg, 94%). The sample was recrystallized from Skellysolve B to give **31** as white crystals. m.p. 179-180°C; tlc: R_f 0.38 (Skellysolve B/ethyl acetate, 3:2); ir (CH_2Cl_2, cast): 2190, 1726, 1715, 1249, 1192, 1111, 1011, 991, 978 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ4.48 (1H, s, H-14), 3.68 (3H, s, C-18 OCH_3), 3.54 (3H, s), 3.25 (3H, s), 3.24 (3H, s), 2.45 (1H, dd, 14.5, 11.5 Hz, H-11β), 2.34 (1H, dt, 12.3 Hz, H-7β), 2.06 (1H, dd, 14.5, 7 Hz, H-11α), 1.89 (1H, dd, 10, 3.5 Hz, H-5), 1.82 (1H, dd, 11, 5 Hz), 1.73 (1H, dd, 11.5, 7 Hz, H-9), 1.70-1.20 (8H, m), 1.19 (3H, s, C-4 CH_3), 1.12 (3H, s, CH_3-16), 1.08 (3H, s, CH_3-17), 0.92 (3H, s, C-10 CH_3); cims (NH_3): 459 (M^+ + 18, 12), 427(13), 416(100), 378(58), 363(15), 346(61), 263(26), 75(30).

(1S,2R,3R,6R,7R)-2-((Z)-2-Acetoxy-3-oxo-4-methylpent-1-enyl)-1,7-dimethyl-3-(1,1-dimethoxymethyl)-3-hydroxyl-7-methoxycarbonylbicyclo[4,4,0]decane 32 and (1S,2R,3R,6R,7R)-1,7-dimethyl-3-(1,1-dimethoxymethyl)-3-hydroxyl-7-methoxycarbonyl-2-(4-oxo-3-acetoxy-2-methylpent-2-enyl)-bicyclo[4,4,0]decane 33

The α-diketone **20** (187.3 mg, 0.44 mmol), acetic anhydride (2 mL), and diisopropylethylamine (4 mL) were placed in a round bottom flask fitted with a condenser. The two phase reaction was refluxed under N_2 for 1.5 h. The reaction was poured on ice/satd $NaHCO_3$ and extracted with Et_2O (3×). The organic extracts were combined, washed with 10% HCl (3×), satd $NaHCO_3$ (2×), brine (2×), dried (Na_2SO_4), and concentrated in vacuo to give a dark yellow oil (198 mg). The crude product was purified by flash column chromatography (Skellysolve B/acetone, 4:1) to give **32** (145 mg, 70%) and **33** (11 mg, 5%). Compound **32**: tlc: R_f 0.27 (Skellysolve B/acetone, 7:3), 0.3 (ethyl ether/benzene, 3:2); ir ($CHCl_3$, cast): 3550, 1759, 1725, 1686, 1640, 1250, 1212, 1070, 755 cm^{-1}, uv (MeOH) λ_{max}: 235 nm (ε 10702); ^1H nmr (400 MHz, $CDCl_3$): δ6.45 (1H, d, 11 Hz, H-11), 4.48 (1H, s, H-14), 3.63 (3H, s, C-18 OCH_3), 3.43 (3H, s, C-14 OCH_3), 3.40 (3H, s, C-14 OCH_3), 3.06 (1H, quintet, 7 Hz, H-15), 2.58 (1H, br s, D_2O exchangeable), 2.56 (1H, d, 11 Hz, H-9), 2.22 (3H, s,

$OOCCH_3$), 2.13 (1H, m), 1.86 (1H, m), 1.76-1.20 (9H, m), 1.16 (3H, d, 7 Hz, CH_3-16), 1.15 (3H, s, C-4 CH_3), 1.12 (3H, d, 7 Hz, CH_3-17), 1.01 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{24}H_{36}O_7$ ($M^+ - CH_4O$): 436.2461, found: 436.2461(2), 394(36), 351(4), 333(3), 291(6), 273(7), 121(10), 75(100); cims (NH_3): 486 (M^+ + 18, 100%); Analysis: calcd for $C_{25}H_{40}O_8$: C 64.08, H 8.6, found: C 64.37, H 8.63.

Compound **33**; oil, tlc: R_f 0.22 (Skellysolve B/acetone, 7:3), 0.22 (ethyl ether/benzene, 3:2); ir ($CHCl_3$, cast): 3544 (br), 1754, 1723, 1695, 1625, 1249, 1211, 1128, 1068, 750 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ4.36 (1H, s, H-14), 3.67 (3H, s, C-18 OCH_3), 3.60 (3H, s, C-14 OCH_3), 3.45 (3H, s, C-14 OCH_3), 3.06 (1H, dd, 20, 5 Hz), 2.41 (2H, m), 2.28 (3H, s, $OOCCH_3$), 2.17 (3H, s, CH_3-16), 2.12-1.96 (2H, m), 1.76 (3H, s, CH_3-17), 1.58-0.9 (10H, m), 1.12 (3H, s, C-4 CH_3), 0.84 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{24}H_{36}O_7$ ($M^+ - CH_4O$): 436.2461, found 436.2460(7), 393(37), 376(22), 375(11), 333(25), 315(34), 273(18), 263(21), 141(15), 121(23), 75(100); cims (NH_3): 486 (M^+ + 18, 8), 437(29), 405(100).

(1S,5R,6R,9R,12S,14R)-1,5-Dimethyl-9-(1,1-dimethoxymethyl)-10,11-dioxa-12-(1-hydroxyl-2-methylpropyl)-5-methoxycarbonyltricyclo[8,4,6,$0^{9,14}$]tetradecane **36**

Sodium borohydride (9.1 mg, 0.24 mmol) was added slowly over 15 min to a solution of the ketoperoxide **28** (102 mg, 0.24 mmol) in methanol/dichloromethane (4:1). After addition was completed, 1 drop of acetic acid was added, the reaction mixture stirred for 5 min, then the solvent removed *in vacuo*. The residue was partitioned between Et_2O/H_2O. The organic layer was washed with satd $NaHCO_3$ (2×), brine (2×), dried (Na_2SO_4), and concentrated *in vacuo* to yield **36** as a solid (94 mg, 92%). A portion of the product was recrystallized in Et_2O/Skellysolve B to obtain colorless needles. m.p. 134-135°C. The following data were obtained for **36** which was isolated as a mixture of epimers; tlc: R_f 0.37 and 0.33 (Skellysolve B/acetone, 7:3); 0.44 and 0.33 (benzene/acetone, 4:1); ir (CH_2Cl_2, cast): 3537 (br), 1724, 1250, 1192, 1170, 1153, 1125, 1089 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ4.61 (0.6H, s, H-14), 4.59 (0.4H, s, H-14), 4.36 (1H, m, H-12), 3.67 (3H, s, C-18 OCH_3), 3.62 (3H, s, C-14 OCH_3), 3.48 and 3.47 (3H, s, C-14 OCH_3), 3.35 (0.6H, dd, 11.5, 3 Hz, H-13), 3.12 (0.4H, dd, 8.5, 4.5 Hz, H-13), 2.66 (0.6H, br s, D_2O exchangeable), 2.41 (0.4H, br s, D_2O exchangeable), 2.41-2.17 (1H, m), 1.98-1.24 (14H, m), 1.18 (3H, s, C-4 CH_3), 1.03 (3H, d, 7 Hz, CH_3-16), 0.94 (3H, s, C-10 CH_3), 0.85 (3H, d, 7 Hz, CH_3-17); cims (NH_3): 446 (M^+ + 18, 53), 382(100); hrms: m/z calcd for $C_{16}H_{25}O_4$: 281.1746, found 281.1752(M^+-$C_7H_{15}O_3$, 2), 221(1), 203(1), 121(4), 93(2), 75(100).

Hemiacetals 37

Metallic sodium (5 mg) was added to methanol (2 mL) and when the sodium was consumed the solution was added to compound **36** (20 mg, 0.046 mmol) in methanol (2 mL). After 12 h at room temperature one drop of water was added, the solvent evaporated, and the residue dissolved in CH_2Cl_2. The organic layer was washed with H_2O (2×), brine (×), dried (Na_2SO_4), and the solvent removed in vacuo to yield a solid hemiacetal **37** (13.5 mg, 81%). An analytical sample was obtained by recrystallization from Skellysolve B. m.p. 99-100°C; tlc: R_f 0.2 (benzene/acetone, 4:1), 0.35 (Skellysolve B/acetone, 3:2); ir (CH_2Cl_2, cast): 3480 (br), 2760, 1725, 1248, 1121, 1070 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 9.7 (0.15H, t, 2.5 Hz, H-12), 5.64 (0.15H, m, H-12), 5.43 (0.7H, m, H-12); hrms: m/z calcd for $C_{19}H_{30}O_5$: 338.2085, found: 338.2093 (M^+ - H_2O, 0.25), 324(9), 281(42), 221(10), 121(14), 75(100); cims (NH_3): 374 (M^+ + 18,17), 356(18), 310(100).

(1S,5R,6R,9R,11S,13R)-11-Acetoxy-1,5-dimethyl-9-(1,1-dimethoxymethyl)-5-methoxycarbonyl-10-oxatricyclo-$[7,4,0,0^{9,13}]$tridecane 38 and (1S,5R,6R,9R,11R,13R)-11-acetoxy-1,5-dimethyl-9-(1,1-dimethoxymethyl)-5-methoxycarbonyl-10-oxatricyclo$[7,4,0,0^{9,13}]$tridecane 39

The hemiacetal **37** (10.8 mg, 0.03 mmol) and acetic anhydride (10 drops) in triethylamine (2 mL) were stirred at r.t. for 36 h. The solution was poured into cold satd $NaHCO_3$ and extracted with Et_2O (2×). The ether extract was washed with 10% HCl (2×), satd $NaHCO_3$ (2×), H_2O (×), brine (2×), dried (Na_2SO_4), and evaporated to give a yellow oil. Purification by flash chromatography (Skellysolve B/ethyl acetate, 55:45) furnished the acetate **38** (6.8 mg, 57%) and the acetate **39** (1.6 mg, 14%), each as a colorless oil.

The acetate **38** has the following properties: tlc: R_f 0.36 (Skellysolve B/ethyl acetate, 1:1), 0.57 (dichloromethane/acetone, 85:15); ir (CH_2Cl_2, cast): 1744, 1729, 1241 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ6.37 (1H, d, 5.5 Hz, H-12), 4.55 (1H, s, H-14), 3.7 (3H, s, C-18 OCH_3), 3.51 (3H, s, C-14 OCH_3), 3.38 (3H, s, C-14 OCH_3), 2.46 (1H, ddd, 14, 11.5, 5.5 Hz, H-11β), 2.35 (1H, m, H-7β), 2.07 (3H, s, CH_3COO), 1.95 (1H, dd, 14, 7 Hz, H-11α), 1.54 (1H, dd, 11.5, 7 Hz, 1H, H-9), 1.91-1.21 (10H, m), 1.19 (3H, s, C-4 CH_3), 0.93 (3H, s, C-10 CH_3);

hrms: m/z calcd for $C_{19}H_{31}O_5$ 339.2163, found: 339.2172 ($M^+ - C_2H_3O_2$, 0.6), 323(5), 295(8), 263(100), 221(8), 203(17), 184(8), 156(17), 141(12), 121(13), 75(78); cims (NH_3): 416 (M^+ + 18, 87), 263(100).

The acetate **39** has the following properties: tlc: R_f 0.27 (Skellysolve B/ethyl acetate, 1:1), 0.45 (dichloromethane/acetone, 85:15); ir (CH_2Cl_2, cast): 1744, 1727, 1239, 1127, 1070, 969 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ6.16 (1H, t, 5.5 Hz, H-12), 4.5 (1H, s, H-14), 3.65 (3H, s, C-18 OCH_3), 3.43 (3H, s, C-14 OCH_3), 3.37 (3H, s, C-14 OCH_3), 2.26 (1H, br d, 12, 3 Hz, H-7β), 2.20 (1H, ddd, 17, 11, 5.5 Hz, H-11β), 2.06 (3H, s, CH_3COO), 2.0 (1H, dt, 17, 5.5 Hz, H-11α), 1.85-1.18 (11H, m), 1.16 (3H, s, C-4 CH_3), 0.94 (3H, s, C-10 CH_3); cims (NH_3): 416 (M^+ + 18, 2), 356(3), 312(17).

(1S,5R,6R,9R,11S,13R)-1,5-Dimethyl-9-formyl-5-methoxycarbonyl-11-methoxy-10-oxatricyclo[7,4,0,$0^{9,15}$]tridecane **41** and (1S,5R,6R,9R,11R,13R)-1,5-dimethyl-9-formyl-5-methoxylcarbonyl-11-methoxy-10-oxatricyclo[7,4,0,$0^{9,13}$]-tridecane **42**

Methanesulfonyl chloride (0.05 mL) was added to a solution of hemiacetal **37** (14.8 mg, 0.041 mmol), triethylamine (0.1 mL) and CH_2Cl_2 (2 mL) at 0°C. After 4 h at 0°C the solution was warmed up to r.t., then 1 drop of H_2O was added. The solution was stirred for 2 h, then poured onto H_2O, extracted with CH_2Cl_2 (2×). The extract was washed with H_2O (2×), brine (×), dried (Na_2SO_4), and evaporated in vacuo to give a yellow oil. Purification by flash chromatography (Skellysolve B/ethyl acetate, 3:1) afforded the aldehyde **41** (6.2 mg, 47%). An analytical sample was obtained by recrystallization from Skellysolve B. m.p. 109°C; tlc: R_f 0.35 (dichloromethane/acetone, 98:2), 0.34 (Skellysolve B/ethyl acetate, 7:3); $[\alpha]_D$ - 54.9 (c 0.41, $CHCl_3$); ir (CH_2Cl_2, cast): 2760, 1723, 1248, 1173, 1114, 1099, 1066, 966 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ9.82 (1H, d, 1.5 Hz, H-14), 5.24 (1H, t, 5 Hz, H-12, X spin of an ABCX system), 3.64 (3H, s, C-18 OCH_3), 3.39 (3H, s, C-12 OCH_3), 2.44 (1H, dt, 12, 3 Hz, H-7β), 2.24 (1H, complex, C spin of an ABCX system), 1.96 (2H, complex, AB spins of an ABCX system), 1.81 (1H, dd, 12.75, 2.75 Hz, H-5), 1.78-1.12 (9H, m), 1.1 (3H, s, C-4 CH_3), 0.82 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ198.1 (d, C-14), 178.7 (s, C-18), 107.0 (d, C-12), 85.3 (s, C-8), 61.1 (d, C-9), 56.2 (q, C-12 OCH_3), 51.9 (q, C-18 OCH_3), 50.9 (d, C-5), 46.8 (s, C-4), 38.2, 37.1, 36.1 (s, C-16), 31.2, 31.0, 22.5, 17.3 (t, C-2), 15.9 (q, CH_3), 15.4 (q, CH_3); hrms: m/z calcd for $C_{17}H_{27}O_4$ (M^+ - CHO): 295.1902, found 295.1910 (100), 231(4), 203(23), 121(12); cims (NH_3): 342(M^+ + 18,20), 310(100), 292(10).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) on the aldehyde gave the following results: presaturation of H-14 (δ9.82): 7% (H-11β), 7% (C-4 CH_3), 17% (C-10 CH_3); presaturation of C-10 CH_3, (δ0.82): 15% (H-14), 9.5% (H-11β), 20% (C-4 CH_3).

In some cases the aldehyde **42** was formed as a minor component of the crude product. An analytical sample was obtained by recrystallization from Skellysolve B. m.p. 90-91°C; tlc: R_f 0.34 (Skellysolve B/ethyl acetate, 7:3); ir (CH_2Cl_2, cast): 2740, 1725, 1247, 1172, 1102, 1002 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ9.61 (1H, s, H-14), 5.31 (1H, d, 5.5 Hz, H-12), 3.67 (3H, s, C-18 OCH_3), 3.39 (3H, s, C-12 OCH_3), 2.37 (1H, complex, H-7β), 2.18 (1H, dd, 14, 6 Hz, H-11α), 2.06 (1H, ddd, 14.5, 12, 5.5 Hz, H-11β), 1.91 (1H, dd, 12.5, 3 Hz, H-5), 1.78 (1H, dd, 12, 6 Hz, H-9), 1.82-1.73 (1H, m), 1.69-1.21 (8H, m), 1.13 (3H, s, C-4 CH_3), 0.76 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ198.3 (d, C-14), 178.6 (s, C-18), 105.5 (d, C-12), 86.5 (s, C-8), 58.7 (d, C-9), 55.3 (q, C-12 OCH_3), 51.9 (q, C-18 OCH_3), 50.6 (d, C-5), 46.8 (s, C-4, 38.1 (t), 37.1 (t), 35.8 (s, C-10), 32.6 (t), 30.4 (t), 22.7 (t), 17.4 (t, C-2), 16.3 (q), 15.9 (q); hrms: m/z calcd for $C_{17}H_{27}O_4$ (M^+ - CHO): 295.1902, found 295.1911 (100%), 265(3), 203(24), 185(7), 159(8), 121(21).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) gave the following results: presaturation of C-10-CH_3 (δ0.76): 12% (H-14), 7.5% (H-11β), 15% (C-4 CH_3).

(1S,5R,6R,9R,12S,14R)-1,5-Dimethyl-10,11-dioxa-9-ethylenedioxymethyl-12-isopropylcarbonyl-5-methoxycarbonyltricyclo[8,4,0,$0^{9,14}$]tetradecane **43**

A solution of the crude aldehyde **27** (543 mg, 1.43 mmol), ethylene glycol (0.4 mL, 7.15 mmol), triethylorthoformate (0.78 mL, 7.15 mmol), and *p*-toluenesulfonic acid (40 mg) in dry benzene (6 mL) was stirred in an oil bath at 45°C under reduced pressure (160 mm Hg) for 10 h. The dimethyl acetal formed in the reaction was converted to the dioxolane by adding ethylene glycol (0.4 mL) and heating the solution at 80°C for 10 min at atmospheric pressure. The reaction mixture was diluted with CH_2Cl_2, washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and concentrated *in vacuo* to yield an oil. Recrystallization from Et_2O afforded the ketone **43** as white crystals (239.2 mg) and purification of the mother liquors by flash chromatography (dichloromethane/ethyl acetate, 9:1) gave a solid (121.6 mg). The overall yield of the ketone **42** from levopimaric acid is 49% when the reaction sequence is carried out without purification. m.p. 178-179°C; tlc: R_f 0.32 (Skellysolve

B/ethyl acetate, 7:3), 0.45 (dichloromethane/ethyl acetate, 9:1, $[\alpha]_D$ -133.3 (*c* 0.15, $CHCl_3$); ir (CH_2Cl_2, cast): 1722, 1713, 1245, 1171, 1147, 1042 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ5.37 (1H, s, H-14), 4.80 (1H, dd, 11.5, 2.5 Hz, H-12), 4.20-3.84 (4H, complex), 3.68 (3H, s), 2.88 (1H, quintet, 7 Hz, H-15), 2.21 (1H, complex), 1.94 (1H, dt, 12.5, 3 Hz, H-7β), 1.9-0.83 (12H, m), 1.18 (3H, s, C-4 CH_3), 1.12 (3H, d, 7 Hz, CH_3-16), 1.06 (3H, d, 7 Hz, CH_3-17), 1.01 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ210.5 (s, C-13), 178.7 (s, C-18), 105.5 (d, C-14), 86.3 (d, C-12), 81.4 (s, C-8), 65.2 (t), 65.0 (t), 57.4 (d, C-9), 51.9 (q, C-18 OCH_3), 50.9 (d, C-5), 47.4 (s, C-4), 38.1 (t), 36.9 (t), 35.9 (s, C-10), 32.7 (t), 22.3 (t), 22.0 (t), 18.1 (q), 17.6 (t), 17.5 (q), 16.0 (q, two carbons); hrms: m/z calcd for $C_{19}H_{29}O_6$ ($M^+ - C_4H_7O$): 353.1956, found: 353.1965(1), 281(1), 203(1), 121(3), 73(100); cims (NH_3): 442 (M^+ + 18, 24), 424(M^+, 3), 337(100). Analysis: calcd for $C_{23}H_{36}O_7$: C 65.03, H 8.55; Found: C 65.03, H 8.50.

(1S,5R,6R,9R,12S,14R)-1,5-Dimethyl-10,11-dioxa-9-ethylenedioxymethyl-12-(1-hydroxy-2-methylpropyl)-5-methoxycarbonyltricyclo[8,4,0,$0^{9,14}$]tetradecane **44**

Sodium borohydride (225 mg, 5.94 mmol) was added slowly to a stirred solution of ketone **43** (2.52 g, 5.94

mmol) in CH_2Cl_2/MeOH (20 mL, 1:1). After 15 min the addition was completed, then the reaction was quenched with 3 drops of acetic acid, the solvent removed under vacuum and the residue partitioned in Et_2O/H_2O. The ethereal layer was separated and washed with satd $NaHCO_3$ (2×), H_2O (×), brine (2×), dried ($MgSO_4$), and evaporated in vacuo to yield the epimeric alcohols **44** as a solid. An analytical sample was obtained by recrystallization from Skellysolve B: m.p. 163.5-164.5°C; tlc (both epimers): R_f 0.36 and 0.34 (Skellysolve B/acetone, 7:3), 0.68 and 0.6 (dichloromethane/acetone, 7:3); ir ($CHCl_3$, cast): 3520 (br), 1724, 1249, 1170, 1150, 1125, 1106, 1008, 755 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ5.28 (0.3H, s, H-14), 5.22 (0.7H, s, H-14), 4.34 (0.7H, dt, 11, 3 Hz, H-12), 4.29 (0.3H, ddd, 11, 5.5, 3 Hz, H-12), 3.3 (0.7H, dd, 8, 3 Hz, H-13), 3.18 (0.3H, t, 5.5 Hz, H-13), 2.31 (0.7H, s, D_2O exchangeable), 2.13 (0.3H, s, D_2O exchangeable); hrms: m/z calcd for $C_{19}H_{29}O_6$: 353.1956; found: 353.1964 ($M^+ - C_4H_9O$, 0.3), 321(1), 281(2), 121(3), 73(100); cims (NH_3): 444 ($M^+ + 18$, 25), 426 (M^+, 1), 337(100). Analysis: calcd for $C_{23}H_{38}O_7$: C 64.75, H, 8.98; Found: C 65.11, H 8.93.

Hemiacetals 45

A solution of the crude alcohols **44** and sodium methylate (321 mg, 5.94 mmol) in methanol (30 mL) was stirred for 12 h at r.t. Water (0.1 mL) was added and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O (2×), brine (×), dried ($MgSO_4$), and evaporated in vacuo to give the hemiacetal **45** as a solid. An analytical sample was obtained by recrystallization from Skellysolve B/diisopropyl ether: m.p. 122-123°C, tlc: R_f 0.29 (Skellysolve B/acetone, 3:2), 0.19 (benzene/acetone, 4:1), 0.41 (dichloromethane/acetone, 7:3); ir ($CHCl_3$, cast): 3428 (br), 2720, 1726 (br), 1249, 1172, 1142, 1119, 1070, 947, 755 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ9.74 (0.2H, t, 2.5 Hz, H-12), 5.56 (0.4H, d, 6 Hz, H-12), 5.44 (0.4H, m, H-12), 5.19, 5.11 and 5.06 (1H, s, H-14); hrms: m/z calcd for $C_{19}H_{30}O_6$: 354.2034, Found: 354.2042(3), 281(66), 221(27), 203(21), 121(26), 73(100). Analysis: calcd for $C_{19}H_{30}O_6$: C 64.38, H 8.53; Found: C 64.61, H 8.62.

(1S,5R,6R,9R,11S,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-11-methanesulfonyl-5-methoxycarbonyl-10-oxatricyclo-[7,4,0,0^{9,13}]tridecane 46

To a solution of hemiacetal **45** (10 mg, 0.028 mmol) and triethylamine (0.1 mL, 1.36 mmol) in CH_2Cl_2 in an ice/water bath (5°C) was added methanesulfonyl chloride (0.05 mL, 0.29 mmol). The solution was stirred for 2 h at 5°C, then poured onto cold H_2O, and extracted with Et_2O

(2×). The organic layer was washed with cold 10% HCl (2×), satd $NaHCO_3$ (2×), H_2O (×), brine (2×), dried ($MgSO_4$), and evaporated in vacuo to give a yellow oil (8.9 mg). Purification by flash chromatography (Skellysolve B/acetone, 3:1) yield **46** as a colorless oil (6 mg). tlc: R_f 0.3 (Skellysolve B/acetone, 3:1), 0.49 (benzene/acetone, 3:2); ir (CH_2Cl_2, cast): 1726, 1358, 1335, 1247, 1150, 1143, 1122, 1100, 945 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ5.18 (1H, s, H-14), 5.06 (1H, d, 5.75 Hz, H-12), 4.02-3.94 (2H, m), 3.9-3.78 (2H, m), 3.65 (3H, s, C-18 OCH_3), 3.37 (3H, s, C-12 OSO_2CH_3), 2.38 (1H, dt, 12, 3 Hz, H-7β), 2.34 (1H, ddd, 14.5, 11.5, 5.75 Hz, H-11β), 2.02 (1H, dd, 14.5, 6.75 Hz, H-11α), 1.92 (1H, dd, 11.5, 3 Hz, H-5), 1.81 (1H, dt, 13.5, 5 Hz), 1.94 (1H, dd, 11.5, 6.75 Hz, H-9), 1.78-1.21 (8H, m), 1.16 (3H, s, C-4 CH_3), 0.95 (3H, s, C-10 CH_3); cims (NH_3): 354(61), 337(39), 295(2), 197(8).

(1S,5R,6R,9R,11R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-methoxycarbonyl-10-oxa-11-phenylthiotricyclo-[7,4,0,$0^{9,13}$]tridecane **47**, (1S,5R,6R,9R,11S,13R)-1,5-dimethyl-9-ethylenedioxymethyl-5-methoxycarbonyl-10-oxa-11-phenylthiotricyclo[7,4,0,$0^{9,13}$]tridecane **48**, and (1S,2R,3R,6R,7R)-1,7-dimethyl-2-(2,2-diphenylthioethyl)-3-ethylenedioxymethyl-3-hydroxy-7-methoxycarbonylbicyclo-[4,4,0]decane **49**

A solution of the crude hemiacetal **45**, thiophenol (1.22 mL, 11.88 mmol), and trifluoroacetic acid (3 drops) in CH_2Cl_2 (25 mL) was stirred for 38 h at r.t. The solution was diluted with CH_2Cl_2 and washed with 5% Na_2CO_3 (4×), brine (×), dried ($MgSO_4$), and evaporated in vacuo to yield the mixture of thioacetals as an oil. Purification by flash chromatography (Skellysolve B/acetone, 3:1) gave the hemithioacetals **47** and **48** (1927.3 mg, 72%) as an oil and the thioacetal **49** (189.2 mg, 6%) as an oil.

An analytical sample of the hemithioacetal **47** was obtained by flash chromatography (Skellysolve B/ethyl acetate, 7:3) as an oil. tlc: R_f 0.7 (benzene/acetone, 4:1), 0.44 (Skellysolve B/acetone, 7:3), 0.41 (Skellysolve B/ethyl acetate, 7:3); $[\alpha]_D$ +80.3 (c 0.11, $CHCl_3$); ir (CH_2Cl_2, cast): 3045, 1725, 1580, 1246, 1143, 1122, 1110, 1069, 914, 740, 690 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ7.48 (2H, dd, 8.5, 1.5 Hz, Ar-H), 7.32-7.12 (3H, m, Ar-H), 5.54

(1H, dd, 9, 6.5 Hz, H-12), 5.28 (1H, s, H-14), 4.39 (1H, complex), 4.10-3.71 (3H, complex), 3.67 (3H, s, C-18 OCH$_3$), 2.39 (1H, ddd, 14.5, 11.5, 9 Hz, H-11β), 2.38 (1H, m, H-7β), 2.12 (1H, dt, 11.5, 6.5 Hz, H-11α), 1.91-1.28 (11H, m), 1.16 (3H, s, C-4 CH$_3$), 1.02 (3H, s, C-10 CH$_3$); ^{13}C nmr (CDCl$_3$): δ178.7 (s, C-18), 138.1 (s), 129.7 (d, 2×), 128.8 (d, 2×), 126.0 (d), 105.3 (d, C-14), 89.3 (s, C-12), 84.2 (s, C-8), 66.5 (t), 64.9 (t), 61.8 (d, C-9), 51.9 (q, C-18 OCH$_3$), 51.8 (d, C-5), 47.0 (s, C-4), 39.1 (t), 37.2 (t), 36.3 (t), 35.8 (s, C-10), 31.3 (t), 23.2 (t), 17.5 (t), 16.2 (q), 15.8 (q); hrms: m/z calcd for $C_{25}H_{34}O_5S$ (M$^+$): 446.2117; found: 446.2127(2), 373(51), 337(100), 293(21), 263(39), 215(18), 121(17), 73(85); cims (NH$_3$): 464 (M$^+$ + 18, 0.6), 354(4), 337(3). Analysis: calcd for $C_{25}H_{34}O_5S$: C 67.23, H 7.67; Found: C 67.23, H 7.58.

An analytical sample of the hemithioacetal **48** was obtained by flash chromatography (Skellysolve B/ethyl acetate, 7:3) as an oil: tlc: R$_f$ 0.64 (benzene/acetone, 4:1), 0.39 (Skellysolve B/acetone, 7:3), 0.33 (Skellysolve B/ethyl acetate, 7:3); [α]$_D$ -81.3 (c 0.16, CHCl$_3$); ir (CH$_2$Cl$_2$, cast): 3045, 1725, 1580, 1247, 1145, 1121, 1106, 937, 738, 690 cm^{-1}; ^{1}H nmr (200 MHz, CDCl$_3$): δ7.61-7.5 (2H, m, Ar-H), 7.42-7.28 (3H, m, Ar-H), 5.63 (1H, dd, 8, 1.5 Hz, H-12), 5.22 (1H, s, H-14), 4.08-3.80 (4H, m), 3.67

(3H, s, C-18 OCH_3), 2.72 (1H, ddd, 14.5, 11.5, 8 Hz, H-11β), 2.38 (1H, m, H-7β), 1.84 (1H, ddd, 11.5, 7, 1.5 Hz, H-11α), 1.76-1.22 (11H, m), 1.12 (3H, s, C-4 CH_3), 0.93 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ178.7 (s, C-18), 134.5 (s, Ar), 132.0 (d, Ar, 2×), 128.7 (d, Ar, 2×), 127.0 (d, Ar), 105.5 (d, C-14), 86.8 (d, C-12), 85.0 (s, C-8), 66.2 (t), 64.7 (t), 60.0 (d, C-9), 51.9 (q, C-18 OCH_3), 51.6 (d, C-5), 46.9 (s, C-4), 39.0 (t), 37.1 (t), 35.8 (t), 35.5 (s, C-10), 31.8 (t), 22.9 (t), 17.5 (t), 16.0 (q), 15.8 (q); hrms: m/z calcd for $C_{25}H_{34}O_5S$ (M^+): 446.2117, found: 446.2127(1), 373(37), 337(100), 293(16), 263(26), 215(15), 121(14), 73(78); cims (NH_3): 464 (M^+ + 18, 8), 354(15). Analysis: calcd for $C_{25}H_{34}O_5S$: C 67.23, H 7.67; Found: C 67.14, H 7.74.

The thioacetal **49** shows the following properties: tlc: R_f 0.33 (Skellysolve B/acetone, 7:3), 0.24 (Skellysolve B/ethyl acetate, 7:3); ir ($CHCl_3$, cast): 3512 (br), 3056, 1723, 1582, 1248, 1141, 1117, 1026, 759, 741, 691 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ7.54 (2H, dd, 8, 1.5 Hz, Ar-H), 7.46 (2H, dd, 8, 1.5 Hz, Ar-H), 7.36-7.19 (6H, m, Ar-H), 4.99 (1H, s, H-14), 4.96 (1H, dd, 9.5, 5.75 Hz, H-12), 3.87-3.66 (4H, m), 3.66 (3H, s, C-18 OCH_3), 2.83 (1H, ddd, 15.5, 6.75, 5.5 Hz, H-11), 2.51 (1H, s, D_2O exchangeable), 2.1 (1H, dd, 10, 3 Hz, H-5), 2.05 (1H, dd, 7, 2.75 Hz, H-9), 1.82 (1H, ddd, 15.5, 9.5, 2.75 Hz, H-11), 1.95-1.16 (10H, m), 1.1 (3H, s, C-4 CH_3), 0.83 (3H, s, C-10 CH_3); lrms: 447(7), 429(15), 373(29), 337(89), 293(14), 263(13), 215(14), 149(17), 121(30), 110(23), 109(19), 73(100).

A solution of the thioacetal **49** (189.2 mg, 0.34 mmol) and trifluoroacetic acid (1 drop) in CH_2Cl_2 (2 mL) was stirred at r.t. for 78 h. The reaction was worked up and purified as described above to yield the hemithioacetals **48** and **49** (72.1 mg) as an oil. The overall yield from the ketoperoxide **43** is 75%.

(1S,5R,6R,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-methoxycarbonyl-10-oxa-11-phenylsulfinyltricyclo-[7,4,0,$0^{9,13}$]tridecane 50

A solution of *m*-chloroperbenzoic acid (188.2 mg, 1.09 mmol) in CH_2Cl_2 (3 mL) was added to a cooled solution (ice bath) of hemithioacetals (468.3 mg, 1.05 mmol) in CH_2Cl_2 (8 mL). The solution was stirred for 15 min, then diluted with CH_2Cl_2, and washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated *in vacuo* to give the sulfoxide **50** (462.5 mg) as an oil. Purification by flash chromatography (benzene/acetone, 4:1) afforded the sulfoxides **50-α** and **50-β** as an oil.

The sulfoxide **50-β** has the following properties: tlc: R_f 0.36 (benzene/acetone, 4:1), 0.35 (Skellysolve

B/acetone, 3:2); ir (CH_2Cl_2, cast): 1729, 1580, 1242, 1120, 1105, 1029, 972, 751, 685 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.75 (2H, dd, 8, 1.5 Hz, Ar-H), 7.56-7.46 (3H, m, Ar-H), 5.17 (1H, s, H-14), 4.65 (1H, dd, 8, 6.5 Hz, H-12), 4.26 (1H, m), 4.02-3.85 (3H, m), 3.66 (3H, s, C-18 OCH_3), 2.85 (1H, ddd, 14, 11.5, 8 Hz, H-11β), 2.31 (1H, dt, 11.75, 3 Hz, H-7β), 2.16 (1H, dt, 11.5, 6.5 Hz, H-11α), 1.88-1.23 (11H, m), 1.17 (3H, s, C-4 CH_3), 1.05 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{22}H_{29}O_4S$ ($M^+ - C_3H_5O_2$): 389.1778, found: 389.1787(10), 337(33), 263(35), 203(24), 73(100); cims (NH_3): 354(62), 337(100), 268(7).

The sulfoxide **50-α** presents the following properties: tlc: R_f 0.33 (benzene/acetone, 4:1), 0.39 (Skellysolve B/acetone, 3:2); ir (CH_2Cl_2, cast): 3045, 1723, 1580, 1248, 1121, 1106, 1037, 1026, 745, 730, 690 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.61 (2H, dd, 8, 1.5 Hz, Ar-H), 7.52-7.44 (3H, m, Ar-H), 5.19 (1H, s, H-14), 4.71 (1H, dd, 8, 2 Hz, H-12), 3.89-3.73 (4H, m), 3.67 (3H, s, C-18 OCH_3); 2.36 (1H, dt, 12, 3.5 Hz, H-7β), 2.32-2.2 (2H, complex), 1.96 (1H, dd, 14, 7 Hz), 1.91 (1H, dd, 12.5, 3 Hz, H-5), 1.84-1.23 (9H, m), 1.16 (3H, s, C-4 CH_3), 0.94 (3H, s, C-10 CH_3); cims (NH_3): 480 (M^+ + 18, 0.1), 354(87), 337(100), 252(47), 234(22).

(1S,5R,6R,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-methoxycarbonyl-10-oxatricyclo[7,4,0,$0^{9,13}$]tridec-11-ene 51

A solution of the sulfoxides **50** (462.5 mg, 1 mmol) and triethylphosphite (0.89 mL, 5.2 mmol) in 10 mL of xylenes was refluxed for 2 1/2 h under N_2. The solvent was removed azeotropically with benzene in the rotavaporator. The residue was purified by flash chromatography (Skellysolve B/ethyl acetate, 65:35) to give the enol **51** (225.7 mg, 65% overall yield from the hemithioacetals) as a solid. An analytical sample was obtained by recrystallization from Skellysolve B/diisopropyl ether. m.p. 93-95°C; tlc: R_f 0.41 (benzene/acetone, 4:1), 0.27 (Skellysolve B/ethyl acetate, 7:3); $[\alpha]_D$ -67.7 (*c* 0.13, $CHCl_3$); ir (CH_2Cl_2, cast): 3080, 1723, 1585, 1246, 1146, 1108, 1030, 991, 675 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ6.4 (1H, t, 3.25 Hz, H-12), 5.31 (1H, s, H-14), 5.17 (1H, t, 2.5 Hz, H-11), 4.06-3.76 (4H, m), 3.67 (3H, s, C-18 OCH_3), 3.06 (1H, br s, H-9), 2.42 (1H, dt, 12, 3.25 Hz, H-7β), 1.91-1.18 (10H, m), 1.17 (3H, s, C-4 CH_3), 1.08 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ178.7 (s, C-18), 147.8 (d, C-12), 104.9 (d, C-14), 101.7 (d, C-11), 88.9 (s, C-8), 65.5 (t), 65.0 (t), 64.5 (d, C-9), 51.9 (q, C-18 OCH_3), 51.4 (d, C-5), 46.9 (s, C-4), 39.3 (t), 37.2 (t), 36.2 (s, C-10), 34.6 (t), 23.6 (t), 17.7 (t), 17.5 (q), 15.5 (q); hrms: m/z calcd for $C_{19}H_{28}O_5$ (M^+): 336.1929; found: 336.1936(0.2), 263(22), 262(12), 203(30), 121(11), 95(10), 81(39), 73(100); cims (NH_3): 354 (M^+ + 18, 24), 337(100). Analysis: calcd for $C_{19}H_{28}O_5$: C 67.83, H 8.39; Found: C 67.55, H 8.28.

12,12-Ethylenedioxy-9α-hydroxy-4α-methoxycarbonyldrim-11-al 19

A solution of the enol ether **51** (124.7 mg, 0.37 mmol) in dichloromethane/methanol (10 mL, 1:1) was cooled in a CO_2/acetone bath. Ozone was bubbled through the solution until a pale blue color appeared. Excess ozone was removed with N_2. Methyl sulfide (0.06 mL) was added and the reaction mixture allowed to reach r.t. The solvent was evaporated and the residue dissolved in CH_2Cl_2, washed with H_2O (2×), brine (×), dried ($MgSO_4$), and evaporated *in vacuo* to give the β-hydroxyaldehyde **19** (123.6 mg, 98%) as a solid. An analytical sample was obtained by recrystallization from Skellysolve B/ethyl acetate. m.p. 120-121°C; $[\alpha]_D$ -52.8 (*c* 0.13, $CHCl_3$); tlc: R_f 0.36 (Skellysolve B/acetone, 3:2), 0.3 (dichloromethane/acetone, 9:1), 0.32 (benzene/acetone, 4:1); ir (CH_2Cl_2, cast): 3505 (br), 2755, 1720, 1253, 1122 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): 9.92 (1H, d, 3 Hz, H-11), 5.26

(1H, s, H-12), 4.08-3.86 (4H, m), 3.68 (3H, s, C-13 OCH_3), 2.97 (1H, s, D_2O exchangeable), 2.17 (1H, d, 3 Hz, H-9), 2.15 (1H, dd, 10, 3 Hz, H-5), 1.99 (1H, br d, 13 Hz), 1.82-1.10 (9H, m), 1.29 (3H, s, C-10 CH_3), 1.19 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{18}H_{28}O_6$ (M^+): 340.1878, found: 340.1885(2), 322(2), 295(14), 267(9), 207(10), 121(8), 73(100); cims (NH_3): 358 (M^+ + 18, 100), 341 (M^+ + 1, 11). Analysis: calcd for $C_{18}H_{28}O_6$: C 63.51, H 8.29; Found: C 63.13, H 8.27.

12,12-Ethylenedioxy-4α-methoxycarbonyl-(9βH)-drim-7-en-11-al 52

The β-hydroxyaldehyde **19** (8.5 mg, 0.025 mmol) was added to a 1 M solution of NaOH in methanol (3 mL). The reaction mixture was refluxed under N_2 for 45 min. The pH of the solution was adjusted to 9 with 10% HCl, diluted with water and extracted with CH_2Cl_2 (3×). The extracts were combined and washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and the solvent removed *in vacuo* to give an impure β,γ-unsaturated aldehyde **52** (5.2 mg). An analytical sample was obtained by flash chromatography (Skellysolve B/acetone, 4:1). tlc: R_f 0.32 (Skellysolve B/ethyl acetate, 3:2), 0.24 (Skellysolve B/acetone, 4:1); ir (CH_2Cl_2, cast): 1720, 1708, 1675, 1253, 1195, 1140, 1102, 1072, 845 cm^{-1}; ^1H nmr (200 MHz,

$CDCl_3$): δ9.64 (1H, d, 5 Hz, H-11), 6.19 (1H, t, 3.5 Hz, H-7), 5.16 (1H, s, H-12), 4.09-3.73 (4H, m), 3.68 (3H, s, C-13 OCH_3), 2.63 (1H, d, 5 Hz, H-9), 2.47 (1H, dd, 10.75, 6.5 Hz, H-5), 2.14-2.03 (2H, m, H-6β, H-6α), 1.8-0.82 (6H, m), 1.26 (3H, s, C-4 CH_3), 0.99 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{18}H_{26}O_5$ (M^+): 322.1773, found: 322.1781(5), 293(95), 279(10), 263(11), 262(13), 201(20), 172(13), 139(12), 105(20), 99(17), 91(19), 73(100); cims (NH_3): 340(M^+ + 18, 100), 323(M^+ + 1, 18), 322(M^+, 7).

4α-Methoxycarbonyl-(9βH)-drim-7-en-11,12-dial **54**

A solution of the β,γ-unsaturated aldehyde **52** (3 mg), and catalytic amounts of *p*-toluenesulfonic acid in acetone (3 mL) was stirred for 1/2 h. The reaction was quenched with satd $NaHCO_3$ (1 drop) and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated *in vacuo* to afford *epi*-polygodial **54** as a solid. Purification by flash chromatography (Skellysolve B/ethyl acetate, 3:2) furnished the pure dialdehyde **54** as a solid. tlc: R_f 0.47 (Skellysolve B/acetone, 3:2), 0.39 (Skellysolve/ethyl acetate, 1:1); ir (CH_2Cl_2, cast): 2715, 1724, 1679, 1646, 1249, 1191, 1140, 720 cm^{-1}; uv (CH_3OH) λ_{max}: 228 nm (ε 7443); ^1H nmr (400 MHz, $CDCl_3$): δ9.85 (1H, d, 2.5 Hz, H-11); 9.41 (1H, s, H-12), 7.05 (1H, t, 3.5 Hz, H-9), 3.67 (3H, s, C-13 OCH_3), 3.26 (1H, br s, $\omega_{1/2}$ = 2.5 Hz, H-9), 2.44 (1H, dd, 10.5, 6 Hz, H-5), 2.37-2.31 (2H, complex, H-6β, H-6α), 1.80 (1H, br d, 12 Hz), 1.74-1.14 (5H, m), 1.27 (3H, d, C-4 CH_3), 0.99 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{16}H_{22}O_4$ (M^+): 278.1512; found: 278.1518(3), 250(100), 235(14), 219(16), 201(17), 190(51), 175(25), 161(15), 147(15), 121(26), 105(29), 91(38); cims (NH_3): 296(M^+ + 18, 100), 298(M^+, 2).

12,12-Ethylenedioxy-9α-formyloxy-4α-methoxycarbonyldrim-11-al **56**

A solution of the enol ether **51** (141 mg, 0.42 mmol) from Skellysolve B/dichloromethane (9:1, 10 mL) was cooled in a dry ice/acetone bath. Ozone was bubbled through the solution until a pale blue color appeared. Excess ozone was removed from the solution with N_2. Trimethylphosphite (0.05 mL) was added, the bath removed and the reaction mixture allowed to reach r.t. The mixture was dried ($MgSO_4$), evaporated *in vacuo* and left under vacuum for 2 h to give the crude formate **56** (160.3 mg) as a partly solidified oil. Purification of the crude formate by flash chromatography (benzene/acetone, 9:1) afforded pure **56** as an oil: tlc: R_f 0.53 (benzene/acetone, 4:1), 0.41 (Skellysolve B/acetone, 3:2); ir (CH_2Cl_2, cast): 2755, 1723 (br s), 1254, 1173, 1140 cm^{-1}; ^1H nmr (200 MHz,

$CDCl_3$): δ9.86 (1H, d, 7.5 Hz, H-11), 8.24 (1H, s, C-8 OCHO), 5.45 (1H, s, H-12), 4.04-3.84 (4H, m), 3.68 (3H, s, C-13 OCH_3), 2.88 (1H, d, 2.5 Hz, H-9), 2.44 (1H, dt, 13, 3.5 Hz), 2.26 (1H, dd, 13, 5 Hz), 2.02 (1H, br d, 13 Hz), 1.93-1.16 (8H, m), 1.29 (3H, s, C-10 CH_3), 1.18 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{29}H_{38}O_7$ (M^+): 368.1827; found: 368.1835(0.2), 322(6), 309(9), 295(3), 121(4), 73(100); cims (NH_3): 386(M^+ + 18, 100), 323(20), 278(6).

12,12-Ethylenedioxy-4α-methoxycarbonyldrim-8-en-11-al **53**, 12,12-ethylenedioxy-4α-methoxycarbonyldrim-7-en-11-al **58**, and **52**

A solution of the crude formate **56** (160.3 mg) and DBU (0.19 mL, 1.25 mmol) in benzene (3.5 mL) was refluxed under argon for 1 1/2 h. The reaction mixture was diluted with CH_2Cl_2, washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated *in vacuo* to yield a mixture of the aldehydes **53**, **58**, **52** and the hydroxyaldehyde **19** (113 mg). The ratios of the products as calculated by ^1H nmr was 14%, 23%, 48% and 15% respectively. The ratio of the unsaturated aldehydes changed with changing reaction conditions. β-Hydroxy aldehyde **19** was always found in 10-15% of the mixture.

Purification of the crude product by flash chromatography (benzene/acetone, 95:5) afforded a pure sample of the α,β-unsaturated aldehyde **53** as an oil. tlc: R_f 0.43 (benzene/acetone, 9:1), 0.49 (Skellysolve B/acetone, 3:2), 0.39 (Skellysolve B/ethyl acetate, 1:1); ir (CH_2Cl_2, cast): 2760, 1725, 1680, 1252, 1118, 1102 cm^{-1}; uv (MeOH) λ_{max}: 237 (ε 6650); ^1H nmr (400 MHz, $CDCl_3$): δ10.08 (1H, s, H-11), 5.82 (1H, s, H-12), 4.03-3.90 (4H, m), 3.68 (3H, s), 2.47-2.26 (3H, complex), 2.01 (1H, dd, 12.5, 1.75 Hz, H-5), 1.78-1.50 (5H, m), 1.26 (3H, s), 1.22 (3H, s); hrms: m/z calcd for $C_{18}H_{26}O_5$ (M^+): 322.1773; found: 322.1780(72), 307(23), 293(5), 263(15), 247(14), 217(29), 203(13), 105(16), 73(100).

The β-γ-unsaturated aldehyde **58** was purified by flash chromatography (benzene/acetone, 95:5) to yield a pure sample as a solid: tlc: R_f 0.4 (benzene/acetone, 9:1), 0.47 (Skellysolve B/acetone, 3:2), 0.38 (Skellysolve B/ethyl acetate, 1:1); ir (CH_2Cl_2, cast): 3005, 2740, 1719, 1249, 1180, 1144, 1101, 1076, 840, 810 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ9.57 (1H, d, 5.5 Hz, H-11), 6.14 (1H, ddd, 5.5, 2.5, 2 Hz, H-7), 5.17 (1H, s, H-12), 4.02-3.72 (4H, m), 3.65 (3H, s, C-13 OCH_3), 2.8 (1H, dddd, 5.5, 4, 2.5, 2 Hz, H-9), 2.18 (1H, dddd, 18, 12.25, 4, 2 Hz, H-6β), 2.01 (1H, dd, 12.75, 4.25 Hz, H-5), 1.85 (1H, dddd, 18, 5.5, 4.25, 2 Hz, H-6α), 1.8-1.33 (6H, m), 1.28 (3H, s, C-10 CH_3), 1.15 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{18}H_{26}O_5$ (M^+): 322.1773; found: 322.1780(13), 294(39), 293(34), 279(10), 263(8), 247(7), 172(11), 154(19), 139(18), 105(17), 91(19), 73(100).

The β,γ-unsaturated aldehyde **52** and the β-hydroxyaldehyde **19** are also isolated from this reaction and present the properties previously described.

4α-Methoxycarbonylpolygodial **59**

A solution of the β,γ-unsaturated aldehyde **58** (4 mg, 0.012 mmol) and a cat. amount of p-toluenesulfonic acid in acetone (2 mL) was stirred for 2 h. The reaction was quenched with satd $NaHCO_3$ (1 drop), and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2/H_2O and washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and the solvent removed to yield compound **59** (3.2 mg, 96%) as a solid. An analytical sample was obtained by flash chromatography (Skellysolve B/ethyl acetate, 3:2). tlc: R_f 0.44 (Skellysolve B/acetone, 3:2), 0.32 (Skellysolve B/ethyl acetate, 1:1); ir (CH_2Cl_2, cast): 2726, 1723, 1679, 1642, 1247, 1189, 1142, 1107, 1069, 1010, 727 cm^{-1}; uv (MeOH) λ_{max}: 223 (ε5681); ^1H nmr (400 MHz, $CDCl_3$): δ9.54 (1H, d, 4 Hz, H-11), 9.46 (1H, s, H-12), 7.08 (1H, ddd, 5.5, 2, 2 Hz, H-7), 3.69 (3H, s, C-13 OCH_3), 2.92 (1H,dddd, 14, 3.5, 2, 2 Hz, H-9), 2.40 (1H, dddd, 19.25, 11.75, 3.75, 2 Hz, H-6β), 2.21 (1H, dddd, 19.25, 5.5, 4, 2 Hz, H-6α), 2.09 (1H, dd, 11.5, 4

Hz, H-5), 1.9 (1H, br d, 11.5 Hz), 1.82-1.24 (5H, m), 1.31 (3H, s), 0.99 (3H, s); hrms: m/z calcd for $C_{16}H_{22}O_4$ (M^+): 278.1512; found: 278.1518(21), 276(2), 250(70), 249(10), 236(17), 205(12), 190(41), 175(23), 109(100); cims (NH_3): 296(M^+ + 18, 100), 264(54).

(1S,5R,6R,9R,12S,14R)-1,5-Dimethyl-10,11-dioxa-12-isopropylcarbonyl-5-methoxycarbonyl-9-trimethylenedioxymethyltricyclo[8,4,0,$0^{9,14}$]tetradecane **60**

A solution of the ketoaldehyde **27**(273.6 mg, 0.718 mmol), trimethylorthoformate (0.39 mL, 3.59 mmol), 1,3-propanediol (0.26 mL, 3.59 mmol) and cat. amount of *p*-toluenesulfonic acid in benzene (3 mL) was warmed to 45°C in an oil bath under mild vacuum (160 mm Hg). When all the solution had disappeared, the reaction mixture was refluxed for 15 min. The solution was diluted with CH_2Cl_2, washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and the solvent removed to give the crude dioxane **60** (298.4 mg, 95%) as an oil. Purification by flash chromatography (Skellysolve B/ethyl ether, 3:2) furnished a pure sample. tlc: 0.42 (dichloromethane/acetone, 95:5), 0.23 (Skellysolve B/ethyl acetate, 7:3), 0.30 (dichloromethane/ethyl acetate, 9:1); ir (CH_2Cl_2, cast): 1722, 1248, 1152, 1121, 1108, 1021, 936, 754 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ4.81 (1H, s, H-14), 4.72 (1H, dd, 11.5, 3.5 Hz, H-12), 4.28 (1H, complex), 4.1 (1H, complex), 3.81 (1H, complex), 3.67 (3H, s, C-18 OCH_3), 3.65 (1H, complex), 3.02 (1H, quintet, 7 Hz, H-15), 2.23-2.1 (2H, m), 1.94 (1H, dt, 13, 3 Hz, H-7β), 1.85 (1H, dd, 12.5, 2.5 Hz, H-5), 1.78-0.98 (12H, m), 1.17 (3H, s, C-4 CH_3), 1.09 (3H, d, 7 Hz, CH_3-16), 1.07 (3H, d, 7 Hz, CH_3-17), 0.93 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{24}H_{38}O_7$ (M^+): 438.2607; found: 438.2617(0.1), 367(4), 307(2), 291(3), 231(5), 129(4), 121(3), 87(100), 71(12); cims (NH_3): 456(M^+ + 18, 100), 438(M^+, 6).

(1S,5R,6R,9R,13R)-1,5-Dimethyl-5-methoxycarbonyl-10-oxa-11-phenylthio-9-trimethylenedioxymethyltricyclo-[7,4,0,$0^{9,13}$]tridecane **61**

Sodium borohydride (52.2 mg, 1.38 mmol) was added in parts to a solution of the ketone **60** (570 mg, 1.38 mmol) in dichloromethane/methanol (1:3, 4 mL). Acetic acid (3 drops) was added to the reaction mixture after 15 min, then the solvent was removed *in vacuo* and the residue dissolved in Et_2O/H_2O. The organic layer was separated and washed with satd $NaHCO_3$ (2×), brine (2×), dried ($MgSO_4$), and evaporated to obtain the epimeric mixture of alcohol as a yellow oil.

The solution of the crude alcohol and sodium methylate (74.5 mg, 1.38 mmol) in methanol (6 mL) was stirred at r.t. for 24 h. H_2O (3 drops) was added and the solvent removed. The oily residue was dissolved in CH_2Cl_2 and washed with H_2O (2×), brine (2×), dried ($MgSO_4$), and the solvent removed in vacuo to yield the hemiacetal as an oil.

A solution of the crude hemiacetal, thiophenol (0.3 mL, 29 mmol) and a cat. amount of trifluoroacetic acid in CH_2Cl_2 (8 mL) was stirred at r.t. for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with 5% Na_2CO_3 (4×), brine (2×), dried ($MgSO_4$), and evaporated in vacuo to give the hemithioacetals **61** (437 mg) as a yellow oil. Purification of the crude product by flash chromatography (dichloromethane/ethyl acetate, 95:5) gave the hemithioacetals **61** (200.0 mg, 32% from the ketone) as a colorless oil. tlc: R_f (same for both epimers) 0.3 (dichloromethane/ethyl acetate, 94:6), 0.4 (dichloromethane/acetone, 96:4); ir (CH_2Cl_2, cast): 3045, 1725, 1596, 1247, 1120, 1108, 1070, 1035, 1015, 958, 738, 670 cm^{-1}; the ^1H nmr shows that the mixture is present in a ratio of 1:3.5 of the β to α-hemithioacetal, respectively. ^1H nmr (400 MHz, $CDCl_3$): δ5.72 (0.78H, dd, 8.5, 2 Hz, H-12), 5.54 (0.22H, dd, 8, 6.75 Hz, H-12), 4.75 (0.22H, s, H-14), 4.65 (0.78H, s, H-14), 1.18 (0.66H, s, C-4 CH_3), 1.13 (2.34H, s, C-4 CH_3), 0.98 (0.66H, s, C-10 CH_3), 0.86 (2.34H, s, C-10 CH_3); hrms: m/z calcd for

$C_{22}H_{29}O_3S$ ($M^+ - C_4H_7O_2$): 373.1858; found: 373.1837(7), 351(100), 307(12), 275(22), 215(28), 197(9), 187(8), 121(11), 110(11), 87(70), 59(13); cims (NH_3): 478(M^+ + 18, 9), 368(71), 351(100).

(1S,5R,6R,9R,13R)-1,5-Dimethyl-5-methoxycarbonyl-10-oxa-9-trimethylenedioxymethyltricyclo[7,4,0,$0^{9,13}$]tridec-11-ene 62

A solution of *m*-chloroperbenzoic acid (77.2 mg, 0.447 mmol) in CH_2Cl_2 (3 mL) was added to a cooled solution of the hemithioacetals **61** (200.1 mg, 0.434 mmol) in CH_2Cl_2 (6 mL). After 10 min the reaction mixture was diluted with CH_2Cl_2, then washed with 10% $NaHSO_3$ (×), satd $NaHCO_3$ (3×), brine (×), dried ($MgSO_4$), and the solvent removed under vacuum to yield the pure sulfoxides (220.2 mg) as an oil. tlc: R_f 0.29, 0.17 (benzene/acetone, 4:1).

A solution of the crude sulfoxides (220.2 mg) and triethylphosphite (0.37 mL, 2.16 mmol) in xylenes (5 mL) was refluxed for 2 1/2 h under argon. The solvent was azeotropically removed with benzene in the rotavaporator. The oily residue was purified using flash chromatography (Skellysolve B/acetone, 3:1) to obtain the enol ether **62** (105.3 mg, 69% overall yield) as a solid. tlc: R_f 0.47 (benzene/acetone, 4:1), 0.31 (Skellysolve B/acetone, 3:1); ^1H nmr (200 MHz, $CDCl_3$): δ6.45 (1H, t, 3

Hz, H-12), 5.16 (1H, m, H-11), 4.75 (1H, s, H-14), 4.26-4.03 (2H, complex), 3.76 (1H, complex), 3.59 (1H, complex), 3.06 (1H, br s, H-9), 2.42-2.28 (2H, complex), 1.86-1.1 (14H, m), 1.15 (3H, s, C-4 CH_3), 1.0 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{20}H_{30}O_5$ (M^+): 350.2085; found: 350.2093(0.3), 263(7), 262(11), 203(7), 187(2), 121(4), 109(2), 87(100), 81(12); cims (NH_3): 368(M^+ + 18, 15), 359(100), 275(42).

Unsaturated aldehydes **63**

A solution of the enol ether **62** (105.3 mg, 0.3 mmol) in Skellysolve B (8 mL) was cooled in a dry ice/acetone bath. Ozone was bubbled through the solution until a pale blue color appeared. Excess ozone was removed with N_2. Trimethylphosphite (0.1 mL) was added and the reaction mixture allowed to reach r.t., diluted with CH_2Cl_2 and dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The crude residue was left under mild vacuum for 2 h. The crude formate (113.2 mg) was a semisolid.

A solution of the crude formate and DBU (0.09 mL, 0.6 mmol) in dry benzene (5 mL) was refluxed for 2 h under argon. The reaction mixture was diluted with CH_2Cl_2, washed with 10% HCl (2×), satd $NaHCO_3$ (×), brine (×), dried ($MgSO_4$), and the solvent removed under vacuum to give a mixture of the unsaturated aldehydes **63** (67.4 mg) as an oil. tlc: R_f 0.42 (for the α,β-unsaturated aldehyde), 0.38 (for the β,γ-unsaturated aldehydes). The ^{1}H nmr indicates that the crude product is composed of the β-hydroxyaldehyde, α,β-unsaturated aldehyde, 9β-β,γ-unsaturated aldehyde and 9α-β,γ-unsaturated aldehyde in an approximate ratio of 1:1:1.25:1.25 respectively. ^{1}H nmr (200 MHz, $CDCl_3$): characteristic signals for the α,β-unsaturated aldehyde: δ10.08 (s, H-11), 5.43 (s, H-12); for the β-hydroxyaldehyde: δ9.83 (d, 2 Hz, H-11), 4.68 (s, H-12); for the 9β-β,γ-unsaturated aldehyde: 9.68 (d, 4.5 Hz, H-11), 6.04 (m, H-7), 4.89 (s, H-12), 2.85 (m, H-9) and for the 9α-β,γ-unsaturated aldehyde: δ9.62 (d, 5 Hz, H-11), 6.13 (t, 3.75 Hz, H-7), 4.71 (s, H-12), 2.67 (d, 5 Hz, H-9).

12,12-Ethylenedioxy-9α-hydroxy-4α-methoxycarbonyl-drim-7-en-11-al **64**

In a flamed three-neck round-bottom flask, adapted with a L-shaped tube, a N_2 line, and a septum was placed a 35% KH emulsion (59 mg, 0.5 mmol). The oil was removed with Skellysolve B (3×) and 1 mL of THF added. The flask was cooled in an ice bath then the mixture of aldehydes **52**, **53** and **58** (46 mg, 0.14 mmol) in THF (4 mL) were added slowly. The suspension was stirred for 2 h. The MoOPH reagent (99 mg, 0.228 mmol) was placed in the L-shaped tube and the flask placed in a CO_2/acetone bath. The MoOPH reagent was added all at once and the suspension stirred vigorously, while the reaction warmed to -44°C (CO_2/CH_3CN). The mixture was stirred at this temperature for 1 1/2 h, the bath removed, and allowed to warm to 0°C. The reaction was quenched with 10% Na_2SO_3 (1 mL) and stirred until no further change in the organic layer was observed. The two phases were separated and the aqueous layer extracted with H_2O (3×). The ethereal extracts were combined and washed with H_2O (2×), brine (2×), dried ($MgSO_4$), and evaporated *in vacuo* to give an oil (37.1 mg). Purification by flash chromatography (dichloromethane/acetone, 92:8) afforded the hydroxyaldehyde **64** (23.9 mg, 50%) as a solid. An analytical sample obtained by recrystallization from Skellysolve B. m.p. 140-141°C; tlc: R_f 0.27 (benzene/acetone, 9:1), 0.29 (dichloromethane/acetone, 95:5), 0.28 (dichloromethane/ethyl acetate, 85:15); $[\alpha]_D$ -30.7° (*c* 0.13, $CHCl_3$); ir (CH_2Cl_2, cast): 3450 (br), 1714, 1675, 1246, 1181, 1135, 1049, 922 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ9.83 (1H, d, 1 Hz, H-11), 6.29 (1H, dd, 5.25, 2.5 Hz, H-7), 5.17 (1H, s, H-12), 3.92 (1H, d, 1 Hz, D_2O exchangeable), 3.93-3.71 (4H, m), 3.65 (3H, s, C-13 OCH_3), 2.66 (1H, dd, 12, 5 Hz, H-5), 2.19 (1H, ddd, 19, 12, 2.5 Hz, H-6β), 1.96 (1H, dt, 19, 5 Hz, H-6α), 1.91-1.79 (2H, m), 1.63-1.52 (3H, m), 1.31 (3H, s, C-4 CH_3), 1.25 (3H, s, C-10 CH_3), 1.01 (1H, br d, 13 Hz); ^{13}C nmr ($CDCl_3$): δ202.9 (d, C-11), 178.1 (s, C-13), 135.7 (d, C-7), 133.4 (s, C-8), 105.8 (d, C-12), 80.2 (s, C-9), 64.8 (t), 64.5 (t), 51.9 (q, C-13 OCH_3), 46.1 (s, C-4), 41.1 (s, C-10), 37.2 (d, C-5), 36.4 (t), 31.2 (t), 25.6 (t), 17.5 (q, 2×) 17.5 (t); hrms: m/z calcd for $C_{18}H_{26}O_6$ (M^+): 338.1722; found: 338.1730(7), 320(2), 309(80), 277(8), 265(7), 187(15), 159(13), 109(15), 73(100). Analysis: calcd for $C_{18}H_{26}O_6$: C 63.88, H 7.74; Found: C 63.66, H 7.7.

4α-Methoxycarbonylwarburganal **20**

A solution of the monoprotected dialdehyde **64** (14.2 mg, 0.042 mmol) and cat. amount of *p*-toluenesulfonic acid in acetone (3 mL) was stirred for 1 h at r.t. The reaction quenched with satd. $NaHCO_3$ (1 drop) and the solvent removed in the rotavaporator. The residue was dissolved in CH_2Cl_2/H_2O, washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated *in vacuo* to give the dialdehyde **20** (11.2 mg, 90% pure by tlc) as a solid.

The solid was recrystallized from Skellysolve B/dichloromethane to obtain an analytical sample as white crystals. m.p. 101-102°C; tlc: R_f 0.24 (benzene/acetone, 9:1), 0.27 (dichloromethane/ethyl acetate, 85:15); 0.38 (Skellysolve B/acetone, 3:2); $[\alpha]_D$ -135.0 (*c* 0.1, $CHCl_3$);

ir (CH_2Cl_2, cast): 3465, 2720, 1725, 1679, 1639, 1249, 1183, 1137, 1120, 1054, 802 cm^{-1}; uv (MeOH) λ_{max}: 226 (ϵ 6000); ^1H nmr (400 MHz, $CDCl_3$): δ9.77 (1H, d, 1.5 Hz, H-11), 9.44 (1H, s, H-12); 7.22 (1H, dd, 5, 2.5 Hz, H-7), 4.12 (1H, d, 1.5 Hz, D_2O exchangeable), 3.7 (3H, s, C-13 OCH_3), 2.68 (1H, dd, 11.5, 5.5 Hz, H-5), 2.42 (1H, ddd, 20.5, 11.5, 2.5 Hz, H-6α), 2.32 (1H, dt, 20.5, 5 Hz, H-6β), 1.86-1.75 (2H, complex), 1.69-1.53 (3H, m), 1.33 (3H, s, C-4 CH_3), 1.13 (3H, s, C-10 CH_3), 1.07 (1H, ddd, 13, 5, 3 Hz); ^{13}C nmr ($CDCl_3$): δ201.5 (d, C-11), 192.4 (d, C-12), 177.9 (s, C-13), 156.2 (d, C-7), 140.5 (s, C-8), 77.2 (s, C-9), 52.2 (q, C-13 OCH_3), 45.9 (s, C-4), 41.1 (s, C-10), 37.0 (d, C-5), 36.3 (t), 30.5 (t), 27.2 (t, C-6), 17.5 (q), 17.4 (q), 17.2 (d); hrms: m/z calcd for $C_{16}H_{22}O_5$ (M^+): 294.1461; found: 294.1467(3), 276(5), 265(100), 261(16), 223(15), 205(32), 189(15), 187(68), 159(64), 121(78), 109(74), 105(26), 91(30). Analysis: Calcd for $C_{16}H_{22}O_5$: C 65.29, H 7.53; Found: C 65.30, H 7.46.

(1S,5R, 6R,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-hydroxymethyl-10-oxa-11-phenylthiotricyclo[7,4,0,$0^{9,13}$]-tridecane 66

A solution of the ester 65 (849 mg, 1.9 mmol) in THF (4 mL) was slowly added to a suspension of $LiAlH_4$ (144.2

mg, 3.8 mmol) in THF (2 mL) cooled in an ice bath. The suspension was stirred for 1/2 h at 5°C then 1 h at r.t. The excess of lithium aluminum hydride was destroyed by careful addition of H_2O (0.15 mL), 15% NaOH (0.15 mL), H_2O (0.45 mL). The slurry was vigorously stirred until a fine solid formed, dried ($MgSO_4$) and filtered. The white solid was washed with Et_2O (3×), and the solvent removed *in vacuo* to yield an epimeric mixture of the alcohol **66** (730.1 mg, 92%) as a colorless oil. tlc: R_f 0.38 (benzene/acetone, 4:1), 0.43 (Skellysolve B/acetone, 3:2); ir (CH_2Cl_2, cast): 3436 (br), 3050, 1580, 1142, 1122, 1071, 1051, 1025, 937, 739, 693 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ5.34 (0.2H, s, H-14), 5.25 (0.8H, s, H-14), 3.37 (1H, br d, 11 Hz, H-18), 3.11 (1H, br d, 11 Hz, H-18), 1.04 (0.6H, s, C-10 CH_3), 0.93 (2.4H, s, C-10 CH_3), 0.80 (0.6H, s, C-4 CH_3), 0.77 (2.4H, s, C-4 CH_3); hrms: m/z calcd for $C_{24}H_{34}O_4S$ (M^+): 418.2168; found: 418.2177(1), 345(44), 309(98), 265(19), 247(21), 235(35), 217(26), 110(15), 73(100).

(1S,5R,6R,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-formyl-10-oxa-11-phenylthiotricyclo[7,4,0,$0^{9,13}$]tridecane 67

A solution of the epimeric mixture of alcohols **66** (414.4 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of PCC (373.4 mg, 1.73 mmol) in CH_2Cl_2 (10 mL). The suspension stirred for 1 1/2 h at r.t., then diluted with Et_2O (30 mL). The reaction mixture was decanted and the sticky oil washed with Et_2O (3×) until it turned solid. The organic combined extracts were filtered through a pad of Florisil and evaporated to yield an aldehyde **67** (373.4, 90%) as an oil. The ^1H nmr of the products shows signals for both epimers in a ratio 4:1. tlc: R_f 0.45, 0.43 (Skellysolve B/acetone, 7:3), 0.46, 0.4 (Skellysolve B/ethyl acetate, 3:2); ir (CH_2Cl_2, cast): 3050, 2680, 1723, 1580, 1142, 1122, 938, 742, 693 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ9.22, 9.17 (1H, s, H-18), 5.29, 5.19 (1H, s, H-14), 1.09, 1.05, 1.03, 0.94 (6H, s, C-4 and 10 CH_3); hrms: m/z calcd for $C_{24}H_{32}O_4S$ (M^+): 416.2012; found: 416.2021(2), 343(30), 307(100), 233(29), 73(77).

(1S,2R,3R,6S)-1,7-Dimethyl-2-ethyl-3-ethylenedioxymethyl-3-hydroxybicyclo[4.4.0]decane **68**

A mixture of the aldehydes **67** (20.2 mg, 0.048 mmol), ethanol (0.1 mL), 95% hydrazine (0.1 mL) and KOH (0.2 g) in ethylene glycol (2 mL) was placed in an oil bath and warmed slowly to 150°C under N_2. After 3 h at 150°C the condenser was replaced with a take-off condenser and the temperature increased to 210°. The reaction mixture was stirred for 5 h at this temperature while a few drops of a colorless liquid distilled. The solution was cooled, diluted with H_2O, and extracted with Et_2O (3×). The combined extracts were washed with H_2O (2×), brine (2×), dried ($MgSO_4$) and evaporated in vacuo to give a complex mixture (12.8 mg) as an oil. Purification by flash chromatography (Skellysolve B/ethyl acetate, 7:3) gave the alcohol **68** (1.2 mg) as an oil. tlc: R_f 0.35 (Skellysolve B/ethyl acetate, 7:3); ir (CH_2Cl_2, cast): 3565 (br), 1387, 1364, 1340, 1118, 1059, 1045, 1020, 963, 947 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.1 (1H, s, H-14), 4.13-3.85 (4H, m), 2.67 (1H, s, D_2O exchangeable), 2.23 (1H, dt, 11.5, 3 Hz, H-7β), 1.99 (1H, complex), 1.78-1.16 (12H, m), 1.01 (3H, t, 7.5 Hz, CH_3-12), 0.87 (6H, s), 0.81 (3H, s); hrms: m/z calcd for $C_{15}H_{27}O$ ($M^+ - C_3H_5O_2$): 223.2055; found: 223.2062(100), 205(86), 137(40), 123(15), 109(13), 99(15), 95(17), 83(11), 73(96); cims (NH_3): 314(M^+ + 18, 100), 296(M^+, 2), 279(95), 235(15), 217(59).

(1S,5R,6R,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-formyl-10-oxa-11-phenylthiotricyclo[7,4,0,$0^{9,13}$]tridecane p-toluenesulfonyl hydrazone **69**

A solution of the epimeric mixture of aldehydes **67** (96.4 g, 0.231 mmol) and p-tosylhydrazine (47.9 mg, 0.258 mmol) in 98% EtOH (0.5 mL) was refluxed for 1 h under a N_2 atmosphere. The reaction mixture was diluted with methanol and the solvent removed in vacuo to yield **69** as a white solid (quantitative). The ^1H nmr indicates that the epimers are in a ratio of 4:1; tlc: R_f 0.2 (Skellysolve B/ethyl acetate, 7:3), 0.37 (benzene/acetone, 9:1); ir (CH_2Cl_2, cast): 3195, 3058, 1597, 1584, 1359, 1169, 1120, 1022, 814, 738, 696, 579 549 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ6.85, 6.81 (1H, s, H-18), 5.25, 5.16 (1H, s, H-14), 2.44 (3H, s, Ar-CH_3), 1.0, 0.97 (3H, s), 0.98, 0.89 (3H, s); hrms: m/z calcd for $C_{28}H_{35}N_2O_3S_2$ (M^+ - $C_3H_5O_2$): 511.2079; found: 511.2089(1), 475(6), 327(25), 291(89), 217(28), 185(13), 155(17), 109(20), 91(52), 73(100).

(1S,6S,9R,11R,13R)-9-Ethylenedioxymethyl-11-phenylthio-1,5,5-trimethyltricyclo[7,4,0,$0^{9,13}$]tridecane **70** and (1S,6S,9R,11S,13R)-9-ethylenedioxymethyl-11-phenylthio-1,5,5-trimethyltricyclo[7,4,0,$0^{9.13}$]tridecane **71**

A flamed three-neck round-bottom flask was charged with benzoic acid (115.3 mg, 9.44 mmol) and chloroform (1.5 mL) in a N_2 atmosphere. The solution was cooled in an ice bath. A 1 M BH_3/THF solution (0.47 mL, 0.47 mmol) was added slowly by syringe to the cool solution, and the mixture stirred for 1/2 h. A solution of the tosylhydrazone **69** (135 mg, 0.231 mmol) in chloroform (2.5 mL) was added to the hydride reagent and stirred for 1 h in the ice bath, NaOAc•3H$_2$O (64 mg, 0.47 mmol) was added and the ice bath removed. The solution was diluted with DMSO (2 mL), then refluxed for 1 h under N$_2$ atmosphere. The reaction mixture was diluted with CH$_2$Cl$_2$, washed with 5% Na$_2$CO$_3$ ~~(3×),~~ brine (×), dried (MgSO$_4$), and evaporated in the rotavaporator to yield an oil. Purification by flash chromatography (Skellysolve B/ethyl acetate, 85:15) afforded the β-hemithioacetal **70** and α-hemithioacetal **71** (43 mg, 46% from the aldehyde) each as an oil that solidifi~~ed in~~ the fridge.

The β-hemithioacetal **70** was recrystallized from methanol/acetone; m.p. 98.5-99.5°C; tlc: R$_f$ 0.56 (Skellysolve B/ethyl acetate, 7:3), 0.40 (Skellysolve B/acetone, 9:1); [α]$_D$ 65° (c 0.21, CHCl$_3$); ir (CH$_2$Cl$_2$, cast): 3045, 1583, 1390, 1380, 1143, 1123, 1055, 951, 944, 912, 741, 692 cm^{-1}; ^{1}H nmr (400 MHz, CDCl$_3$): δ7.5 (2H, dd, 8, 1.5 Hz, Ar-H), 7.34-7.26 (2H, m, Ar-H), 7.19 (1H, tt, 7.5, 1.5 Hz, Ar-H), 5.56 (1H, dd, 9, 6 Hz, H-12), 5.35 (1H, s, H-14), 4.40 (1H, complex), 4.08-3.76 (1H, complex), 2.44 (1H, m), 2.37 (1H, ddd, 14, 11.5, 9 Hz, H-11β), 2.15 (1H, dt, 11, 6 Hz, H-11α), 1.73 (1H, dd, 14, 6 Hz, H-9), 1.84-0.98 (10H, m), 0.98 (3H, s), 0.87 (3H, s), 0.84 (3H, s); ^{13}C nmr (100 MHz, CDCl$_3$): δ138.2 (s, Ar), 129.8 (d, Ar, 2×), 128.8 (d, Ar, 2×), 126.0 (d, Ar-C), 105.5 (d, C-14), 89.4 (d, C-12), 84.3 (s, C-8), 66.5 (t), 64.8 (t), 62.1 (d, C-9), 57.5 (d, C-5), 42.5 (t), 40.1 (t), 36.8 (t), 36.4 (s, C-10), 33.4 (q, C-18), 33.2 (s, C-4), 31.5 (t), 20.9 (q, C-19), 20.8 (t), 18.6 (t, C-2), 15.9 (q, C-20); hrms: m/z calcd for $C_{24}H_{34}O_3S$ (M^+): 402.2219; found: 402.2228(2), 329(40), 293(100), 249(17), 219(31), 187(12), 149(38), 109(12), 73(72). Analysis: calcd for $C_{24}H_{34}O_3S$: C 71.60, H 8.51; Found: C 71.48, H 8.39.

An analytical sample of the α-hemiacetal 71 was obtained by recrystallization from acetone. m.p. 123-124°C; tlc: R_f 0.47 (Skellysolve B/ethyl acetate, 7:3), 0.28 (Skellysolve B/acetone, 9:1); $[\alpha]_D$ -96 (c 0.32, $CHCl_3$); ir (CH_2Cl_2, cast): 3045, 1580, 1396, 1379, 1121, 1096, 1028, 1015, 929, 751, 691 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.54 (2H, dd, 8, 1.5 Hz, Ar-H), 7.36-7.24 (3H, m, Ar-H), 5.6 (1H, dd, 8, 1.5 Hz, H-12), 5.26 (1H, s, H-14), 4.07-3.80 (4H, complex), 2.68 (1H, ddd, 14.5, 11.75, 8.5 Hz, H-11β), 2.4 (1H, dt, 12, 3 Hz, H-7β), 1.79 (1H, ddd, 12, 7, 1.5 Hz, H-11α), 1.74 (1H, ddd, 14, 6.5, 3 Hz), 1.48 (1H, dd, 14.5, 7 Hz, H-9), 1.67-0.78 (3H, m), 0.89 (3H, s), 0.84 (3H, s), 0.8 (3H, s); ^{13}C nmr ($CDCl_3$): δ132.7 (s, Ar), 132.5 (d, Ar, 2×), 128.6 (d, Ar, 2×), 127.0 (d, Ar), 105.7 (d, C-14), 86.5 (d, C-12), 85.2 (s, C-8), 66.2 (t), 64.7 (t), 60.2 (d, C-9), 57.3 (d, C-5), 42.5 (t), 39.9 (t), 36.2 (t), 36.2 (s, C-10), 33.4

(q, C-18), 33.1 (s, C-4), 32.1(t), 20.9 (q, C-19), 20.7 (t), 18.5 (t, C-2), 15.8 (q, C-20); hrms: m/z calcd for $C_{24}H_{34}O_3S$ (M^+): 402.2219; found: 402.2228(1), 329(24), 293(100), 249(13), 219(20), 201(7), 187(10), 95(14), 73(69). Analysis: calcd for $C_{24}H_{34}O_3S$: C 71.60, H 8.51; Found: C 71.44, H 8.45.

Catecholborane (1 mL, 9 mmol) was added to a solution of the tosylhydrazone **69** (prepared as described above from the aldehyde **67** (109.8 mg, 2.45 mmol) and tosylhydrazine (501.4 mg, 2.7 mmol)) in $CHCl_3$ (7 mL) cooled in an ice bath. The solution was stirred for 1 1/2 h at 5°C, quenched with $NaOAc \cdot 3H_2O$ (2.34 g, 17.1 mmol) then warmed to r.t. The slurry was diluted with DMSO (2 mL) and refluxed for 2 h under a N_2 atmosphere. Work-up and purification as described above gave the epimeric mixture of hemithioacetals **70** and **71** (354.5 mg, 36% from the aldehyde) as an oil.

(1S,5R,6S,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-methanesulfonylmethyl-10-oxa-11-phenylthiotricyclo-[7,4,0,$0^{9,13}$]tridecane 72

Methanesulfonyl chloride (0.04 mL, 0.5 mmol) was added to a cool (ice bath) solution of the epimeric mixture of the alcohol **66** (17.5 mg, 0.042 mmol) and triethylamine (0.08 mL, 0.57 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 1 h at 5°C, diluted with CH_2Cl_2 then washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (2×), dried ($MgSO_4$), and the solution removed *in vacuo* to yield the mesylates (20.5 mg, 98%) as an oil; tlc: R_f 0.56, 0.51 (benzene/acetone, 4:1), 0.29, 0.24 (Skellysolve B/acetone, 7:3); ^1H nmr (80 MHz, $CDCl_3$): δ5.3, 5.23 (1H, s, H-14), 3.14, 3.02 (3H, s, O_3SCH_3), 1.05, 0.93 (3H, s), 0.9, 0.85 (3H, s).

(1S,5R,6S,9R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-10-oxa-11-phenylthio-5-tosylmethyltricyclo[7,4,0,$0^{9.13}$]tridecane 73

Tosyl chloride (47 mg, 0.246 mmol) was added to a solution of the epimeric mixture of the alcohol **66** (51.6 mg, 0.123 mmol) and a catalytic amount of DMAP in pyridine (2 mL). The reaction mixture was stirred for 66 h at r.t. then poured onto a cold, satd solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O (3×). The organic extracts were combined, washed with 10% HCl (3×), satd $NaHCO_3$ (3×), H_2O (×), brine (2×), dried ($MgSO_4$), and the solvent removed *in vacuo* to give the tosylates **73** (68.9 mg, 98%) as a colorless oil. The ^1H nmr of the product indicates that the epimers are in a ratio of 3:2. tlc: R_f 0.52, 0.47 (Skellysolve B/acetone, 3:2), 0.32, 0.21 (Skellysolve B/ethyl acetate, 7:[illegible]); ir (CH_2Cl_2, cast):

3050, 1595, 1585, 1359, 1188, 1176, 1143, 1121, 965, 938, 847, 625, 556 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ5.24, 5.15 (1H, s, H-14), 3.68, 3.64, 3.52, 3.5 (2H, d, 9 Hz, H-18), 2.46, 2.45 (3H, s, Ar-CH_3), 0.98, 0.86 (3H, s, C-10 CH_3), 0.78, 0.73 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{31}H_{40}O_6S_2$ (M^+): 572.2254; found: 572.2266(1), 499(20), 463(57), 389(22), 291(27), 217(30), 110(20), 73(100).

2-Propanesulfonyl chloride

Chlorine was bubbled through a cool, vigorously stirred mixture of 2-propanethiol (10 g, 0.13 mol) and H_2O (100 mL). The temperature of the reaction was maintained between 0-10°C. The addition of chlorine was stopped when the aqueous layer (upper layer) turned greenish yellow. The reaction mixture was extracted with ether (3×) and the organic extracts washed with 5% $NaHSO_3$ (4×), 10% $NaHCO_3$ (2×), dried ($MgSO_4$), and the solvent removed to yield an oil. Distillation of the crude product (66-68°C, 13 mm Hg, reported: b.p. Hg 68-70° 11 mm) afforded the 2-propanesulfonyl chloride (7 mL, 48%) as a colorless oil. ^{1}H nmr (100 MHz, $CDCl_3$): δ3.78 (1H, quintet, 7 Hz), 1.61 (6H, d, 7 Hz).

(1S,5R,6S,9R,11R,13R)-1,5-Dimethyl-9-ethylenedioxymethyl-5-isopropylsulfonylmethyl-10-oxa-11-phenylthiotricyclo-[7,4,0,$0^{9,13}$]tridecane 74 and (1S,5R,6S,9R,11S,13R)-1,5-dimethyl-9-ethylenedioxymethyl-5-isopropylsulfonylmethyl-10-oxa-11-phenylthiotricyclo[7,4,0,$0^{9,13}$]tridecane 75

2-Propanesulfonyl chloride (0.14 mL, 1.25 mmol) was added to a solution of the epimeric mixture of alcohols **66** (105 mg, 0.25 mmol), triethylamine (0.43 mL, 3.25 mmol) in Et_2O (4 mL), cooled in a CO_2/CCl_4 bath. The reaction mixture was kept at -20°C for 2 h, then poured onto a cool solution of $NaHCO_3$. The oily product was extracted with CH_2Cl_2 (3×), washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and removed *in vacuo* to give an oil. Purification by flash chromatography (Skellysolve B/ethyl acetate, 3:2) afforded the β-hemithioacetal **74** and the α-hemithioacetal **75** (111.5 mg, 85%) as an oil.

The β-hemithioacetal **74** shows the following properties: tlc: R_f 0.48 (Skellysolve B/ethyl acetate, 1:1); ir (CH_2Cl_2, cast): 3050, 1580, 1350, 1156, 1144, 1122, 960, 912, 836, 694 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ7.58-7.44 (2H, complex, Ar-H), 7.36-7.12 (3H, complex, Ar-H), 5.56 (1H, dd, 9, 6.5 Hz, H-12), 5.31 (1H, s, H-14), 4.41 (1H, complex), 4.18-3.7 (5H, complex), 3.31 (1H, quintet, 6.5 Hz), 2.49-2.28 (2H, m), 2.12 (1H, dt, 11.5, 5.5 Hz), 1.44 (6H, d, 6.5 Hz), 1.88-1.04 (11H, m), 1.04

(3H, s, C-10 CH_3), 0.89 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{21}H_{35}O_6S$ ($M^+ - C_6H_5S$): 415.2144; found: 415.2154(25), 371(4), 341(12), 291(16), 229(10), 217(14), 135(10), 110(18), 105(11), 73(100).

The α-hemithioacetal **75** shows the following properties: tlc: R_f 0.38 (Skellysolve B/ethyl acetate, 1:1); ir (CH_2Cl_2, cast): 3050, 1580, 1349, 1336, 1177, 1155, 1120, 961, 937, 834, 739, 694 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ7.59-7.48 (2H, complex, Ar-H), 7.39-7.22 (3H, complex, Ar-H), 5.58 (1H, dd, 8.5, 1.5 Hz, H-12), 5.21 (1H, s, H-14), 4.09-3.78 (5H, complex), 3.72 (1H, d, 9 Hz, H-18), 3.31 (1H, quintet, 7 Hz), 2.68 (1H, ddd, 14.5, 11.5, 8.5 Hz, H-11β), 2.4 (1H, m), 1.81 (1H, ddd, 12, 7.5, 1.5 Hz, H-11α), 1.47 (6H, d, 7 Hz), 1.73-1.0 (11H, m), 0.92 (3H, s, C-10 CH_3), 0.89 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{27}H_{40}O_6S_2$ (M^+): 524.2254; found: 524.2267(1), 451(13), 415(45), 371(6), 341(12), 229(10), 136(11), 110(19), 95(13), 73(100).

Compounds 70 and 71

A 0.4 M solution of $LiEt_3BH$/THF (1.3 mL, 0.52 mmol) was added to a solution of the isopropanesulfonate **74** and **75** (68.2 mg, 0.13 mmol) in toluene (1.5 mL). The reaction mixture was stirred in an oil bath (90°C) for 6 h. After this reaction time, 1 drop of H_2O was added. The reaction was diluted with ether, washed with $NaHCO_3$ (2×), H_2O (2×), brine (×), dried ($MgSO_4$), and removed the solvent to give an oil (45 mg). Purification of the crude product by flash chromatography (Skellysolve B/ethyl acetate, 85:15) afforded the hemithioacetals **70** and **71** (33.6 mg, 64%) as an oil which presents the same spectroscopic properties as described above.

(1S,6S,9R,13R)-9-Ethylenedioxymethyl-10-oxa-1,5,5-trimethyltricyclo[7,4,0,$0^{9,13}$]tridec-11-ene **76**

A solution of *m*-chloroperbenzoic acid (259.7 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added to a cooled solution (ice bath) of the hemithioacetals **70** and **71** (605.9 mg, 1.5 mmol) in CH_2Cl_2 (10 mL). The reaction mixture stirred for 15 min at 5°C, diluted with CH_2Cl_2, washed with satd $NaHCO_3$ (2×), brine (2×), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give the sulfoxides (610.5 mg) as an oil. tlc: R_f 0.24, 0.12 (benzene/acetone, 9:1).

A solution of the crude sulfoxides (610.5 mg) and triethylphosphite (7.5 mL, 15 mmol) in xylene (10 mL) was refluxed for 4 h under N_2. The solvent was removed azeotropically with benzene. The residue was purified by flash chromatography (Skellysolve B/ethyl acetate, 3:1) to give the enol ether **76** (287.1 mg, 65%) as a solid. tlc: R_f 0.49 (benzene/acetone, 9:1), 0.34 (Skellysolve B/ethyl

acetate, 7:3); ir (KBr): 3089, 1592, 1387, 1369, 1142, 1122, 1030, 696 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ6.47 (1H, t, 3.5 Hz, H-12), 5.39 (1H, s, H-14), 5.23 (1H, m, H-11), 4.12-3.82 (4H, complex), 3.02 (1H, br s, H-9), 2.51 (1H, dt, 12, 3 Hz, H-7β), 1.91-1.0 (10H, m), 1.05 (3H, s), 0.89 (3H, s), 0.84 (3H, s); ^{13}C nmr ($CDCl_3$): δ147.7 (d, C-11), 105.3 (d, C-14), 102.2 (d, C-12), 89.2 (s, C-8), 65.5 (t), 65.0 (t), 64.8 (d, C-9), 57.1 (d, C-5), 42.8 (t), 40.3 (t), 36.8 (s, C-10), 35.3 (t), 33.5 (q, CH_3-18), 33.2 (s, C-4), 21.4 (t), 20.7 (q, CH_3-19), 18.6 (t, C-2), 17.5 (q, CH_3-20); hrms: m/z calcd for $C_{18}H_{28}O_3$ (M^+): 292.2031; found: 292.2038(2), 219(30), 203(7), 149(2), 137(4), 125(14), 81(46), 73(100), 69(19).

12,12-Ethylenedioxy-9α-hydroxydrim-7-en-11-al **78**

A solution of the enol ether **76** (62.3 mg, 0.213 mmol) in ethyl acetate (6 mL) was cooled in a CO_2/acetone bath. Ozone was bubbled through the solution until a pale blue color appeared. Excess ozone was removed with N_2. Triethylphosphite (0.1 mL) was added and the reaction mixture allowed to reach r.t. The solvent was evaporated in vacuo and the residue left under vacuum for 2 h. The formate **77** was identified as follows: tlc: R_f 0.41 (dichloromethane/acetone, 96:4), 0.41 (benzene/acetone, 9:1); ^{1}H nmr (100 MHz, $CDCl_3$): δ9.88 (1H, d, 3 Hz, H-11), 8.24 (1H, s, OCHO), 5.51 (1H, s, H-12), 2.83 (1H, d, 3 Hz, H-9), 1.29 (3H, s, CH_3-15), 0.9 (3H, s), 0.85 (3H,s).

A solution of the crude formate **77**, DBU (0.063 mL, 0.42 mmol) in dry benzene (3 mL) was refluxed under argon for 1 1/2 h. The reaction mixture was diluted with Et_2O, washed with 10% HCl (2×), with $NaHCO_3$ (×), brine (2×), dried ($MgSO_4$), and the ether evaporated in vacuo to give a mixture of unsaturated aldehydes (50.4 mg). In a flamed three-neck, round bottom flask, adapted with a L-shaped tube, a N_2 line and a septum was placed a 35% KH emulsion (50 mg). The oil was removed with Skellysolve B (3×) and 1 mL of THF added. The flask was cooled in an ice bath, then the crude aldehydes in THF (1 mL) were added slowly to the slurry and the mixture stirred for 2 h at 5°C. The MoOPH reagent (118 mg, 0.27 mmol) was placed in the L-shaped tube and the flask cooled in a CO_2/acetone bath. The MoOPH was added all at once, and the suspension stirred vigorously, then warmed slowly to -44°C (CO_2/CH_3CN) and stirred for 1 h. The bath was removed and the reaction was quenched with 10% Na_2SO_3 (1 mL) at 0°C. The two phase solution was stirred until no change in color in the organic layer was observed. The two phases were separated and the aqueous layer was extracted with Et_2O (3×), washed with H_2O (3×), brine (2×), and dried ($MgSO_4$). The Et_2O solution was filtered and evaporated in *vacuo* to yield the crude hydroxyaldehyde **78** (37.5 mg). Purification by flash chromatography (dichloromethane/acetone, 97:3) gave the hydroxyaldehyde **78** as a solid. tlc: R_f 0.42 (dichloromethane/acetone, 96:4), 0.39 (benzene/acetone, 9:1); ir (CH_2Cl_2, cast): 3460, 1713, 1387, 1362, 1111 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ9.85 (1H, d, 1 Hz, H-11), 6.36 (1H, dd, 5, 2.5 Hz, H-7), 5.22 (1H, s, H-12), 3.9 (1H, d, 1 Hz, D_2O exchangeable), 3.99-3.85 (4H, m), 2.28 (1H, dt, 19, 5 Hz, H-6α), 2.11 (1H, ddd, 19, 12, 2.5 Hz, H-6β), 1.89 (1H, dd, 12, 5 Hz, H-5), 1.77 (1H, td, 13, 4.5 Hz), 1.53 (1H, dt, 13.5, 3 Hz), 1.49-1.0 (4H, m), 1.22 (3H, s), 0.97 (3H, s), 0.91 (3H, s); ^{13}C nmr ($CDCl_3$): δ203.5 (d, C-11), 136.6 (d, C-7), 134.2 (s, C-8); 106.1 (d, C-12), 77.9 (s, C-9), 64.8 (t), 64.5 (t), 41.6 (d, C-5), 41.5 (t), 41.4 (s, C-10), 33.1 (q, C-13), 33.0 (s, C-4), 31.9 (t), 24.3 (t), 22.2 (q, C-14), 18.0 (t, C-2), 17.2 (q, C-15); hrms: m/z calcd for $C_{17}H_{26}O_4$ (M^+): 294.1824; found: 294.1831(6), 276(2), 266(11), 265(58), 221(10), 203(4), 157(6), 109(23), 105(11), 73(100), 69(12).

Warburganal (**1**)

A solution of the crude hydroxyaldehyde **78** (37.5 mg) and a cat. amount of *p*-toluenesulfonic acid in acetone (4 mL) was stirred at r.t. for 1 h. The reaction was quenched with satd. $NaHCO_3$ (1 drop), the solvent removed and the residue diluted with CH_2Cl_2. The organic solution was washed with satd. $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated in vacuo to give the crude product (30.4 mg) as an oil. Purification by flash chromatography (dichloromethane/acetone, 97:3) gave an impure sample of polygodial (**3**) (3.9 mg) and warburganal (**1**) (7.5 mg, 14% overall yield from the enol ether **76**) as a solid. An analytical sample was obtained by recrystallization from Skellysolve B. m.p. 106-107°C; tlc: R_f 0.37 (dichloromethane/acetone, 96:4), 0.4 (benzene/acetone, 9:1); $[\alpha]_D$ -243° (c 0.037, $CHCl_3$); ir (CH_2Cl_2, cast): 3479, 3406, 1720, 1682, 1638, 1360, 1357, 1129, 803 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ9.76 (1H, d, 1 Hz, H-11), 9.43 (1H, s, H-12), 7.28 (1H, dd, 5, 2.5 Hz, H-7), 4.09 (1H, d, 1 Hz, D_2O exchangeable), 2.59 (1H, dt, 21.5, 5 Hz, H-6α), 2.35 (1H, ddd, 21.5, 12, 2.5 Hz, H-6β), 1.9 (1H, dd, 12, 5 Hz, H-5), 1.75-1.22 (6H, m), 1.1 (3H, s), 1.0 (3H, s), 0.95 (3H, s); ^{13}C nmr ($CDCl_3$): δ202.0 (d, C-12), 192.5 (d, C-11), 157.2 (d, C-7), 140.5 (s, C-8), 77.1 (s, C-9), 41.7 (d, C-5), 41.4 (s, C-10), 41.3 (t, C-3), 33.0 (s, C-4), 33.0 (q, C-13), 31.2 (t, C-1), 25.9 (t, C-6), 22.0 (q, C-14), 17.7 (t, C-2), 17.0 (q, C-15); hrms: m/z calcd for $C_{15}H_{22}O_3$ (M^+): 250.1563; found: 250.1569(8), 232(7), 222(31), 221(92), 189(18), 161(7), 151(8), 135(7), 124(43), 123(20), 109(100), 105(41), 91(26), 69(42).

(1S,5R,6R,9R,13R)-11-Benzyloxy-1,5-dimethyl-9-ethylenedioxymethyl-5-methoxycarbonyl-10-oxatricyclo[7,4,0,0^{9,13}]-tridecane 79

A solution of the hemiacetal **45** (351.6 mg, 0.99 mmol), benzyl alcohol (0.31 mL, 3.0 mmol) and a cat. amount of trifluoroacetic acid in CH_2Cl_2 (6 mL) was stirred for 22 h at r.t. The reaction mixture was diluted with benzene and all the organic solvents were removed *in vacuo*. The residue was purified by flash chromatography (Skellysolve B/acetone, 4:1) to give the benzylic acetal **79** (375.3 mg, 85%) as a solid. The ratio of the α and β epimers at C-12 was *ca.* 6:1 respectively. Starting with the ketoperoxide and carrying out the sequence of reactions previously described give the benzylic acetal **79** in 80% overall. Analytical sample **79**-α was obtained by recrystallization from Skellysolve B/ethyl ether. m.p. 137-138°C; tlc: R_f 0.3 (Skellysolve B/acetone[illegible] 4:1), 0.38 (dichloromethane/acetone, 95:5), 0.39 (benzene/acetone, 9:1); $[\alpha]_D$ -59.2 (*c* 1.06, $CHCl_3$); ir (CH_2Cl_2, cast): 3050, 1726, 1248, 1142, 1123, 1109, 1094, 1070, 946, 732, 695 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ7.38-7.22 (5H, m, Ar-H), 5.25 (1H, d, 6 Hz, H-12), 5.17 (1H, s, H-14), 4.8 (1H, d, 11.5 Hz, Ar-CH_2O), 4.46 (1H, d, 11.5 Hz, Ar-CH_2O), 4.02-3.74 (4H, complex), 3.62 (3H, s, C-18 OCH_3), 2.36 (1H, dt, 12, 3 Hz, H-7β), 2.33 (1H, ddd, 14, 11.5, 6 Hz, H-11β), 2.07 (1H, dd, 14.5, 7 Hz, H-11α), 1.88 (1H, dd, 9.5, 3 Hz, H-5), 1.78 (1H, td, 13, 5 Hz), 1.61 (1H, dd, 11.5, 6.5 Hz, H-9), 1.7-1.08 (9H, m), 1.11 (3H, s, C-4 CH_3), 0.91 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ178.7 (s, C-18), 138.7 (s, Ar), 128.2 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.3 (d, Ar), 105.5 (d, C-4), 104.5 (d, C-12), 84.5 (s, C-8), 69.3 (t, $ArCH_2O$), 66.1 (d), 64.6 (d), 59.1 (d, C-9), 51.8 (q, C-18OCH_3), 51.7 (d, C-5), 47.1 (t, C-4), 39.3 (t), 37.3 (t), 36.2 (t), 35.7 (s, C-10), 31.1 (t), 23.2 (t, C-6), 17.6 (t, C-2), 16.1 (q), 15.9 (q); hrms: m/z calcd for $C_{23}H_{31}O_4$ ($M^+ - C_3H_5O_2$): 371.2214; found: 371.2222(23), 279(1), 219(4), 181(2), 121(3), 91(100), 83(14). Analysis: calcd for $C_{26}H_{36}O_6$: C 70.24, H 8.16; Found: C 70.34, H 8.23.

(1S,5R,6R,9R,13R)-11-Benzyloxy-5-carboxy-1,5-dimethyl-9-ethylenedioxymethyl-10-oxatricyclo[7,4,0,$0^{9,13}$]tridecane 80

Potassium *tert*-butoxide (404 mg, 3.6 mmol) was added to a solution of the methyl ester **79** (181.8 mg, 0.409 mmol) and water (0.016 mL, 0.9 mmol) in THF (4 mL) cooled in an ice bath. The ice bath was removed after 15 min. The slurry was stirred for 1 1/2 h at r.t. The reaction was quenched by addition of ice, diluted with ether, and the layers separated. The aqueous phase was acidified with 10% HCl to pH 3 and extracted with Et_2O (3×). The organic extracts were mixed, washed with H_2O (2×), brine (2×), dried ($MgSO_4$), and evaporated in vacuo to give the acid **80** (170.8 mg, 97%) as a solid. Recrystallization from Skellysolve B/acetone gave a pure acid as white crystals. m.p. 187-190°C; tlc: R_f 0.20 (Skellysolve B/acetone, 7:3); ir (CH_2Cl_2, cast): 3520-2240 (br), 1693, 1141, 1121, 1094, 1069, 1003, 946, 933, 754 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 7.38-7.28 (5H, m, Ar-H), 5.26 (1H, d, 5.5 Hz, H-12), 5.19 (1H, s, H-14), 4.81 (1H, d, 11.5 Hz, $ArCH_2O-$), 4.47 (1H, d, 11.5 Hz, $ArCH_2O-$), 4.01-3.72 (4H, complex), 2.4 (1H, dt, 12, 2.5 Hz, H-7β), 2.36 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.09 (1H, dd, 14.5, 7 Hz, H-11α), 1.96-1.18 (11H, m), 1.13 (3H, s, C-4 CH_3), 0.92 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{22}H_{29}O_4$ ($M^+ - C_3H_5O_2$): 357.2087; found: 357.2066(20), 237(2), 219(4), 121(2), 91(100), 73(15); cims (NH_3): 430(M^+, 0.1), 357(3), 340(35), 323(100).

Formation of the isomeric mixture of olefin 82

A solution of the acid **80** (24.9 mg, 0.058 mmol), thionyl chloride (1 drop) and pyridine (1 drop) in dry ethyl ether (4 mL) was stirred for 1 h at room temperature, then 2 h at reflux. The solution was diluted with CH_2Cl_2, washed with 1% NaOH (2×), brine (2×), and dried ($MgSO_4$). Removal of the solvent yield an oil (27.4 mg).

A solution of sodium azide (5.6 mg, 0.087 mmol) in water (1 mL) was added to a cooled (0°C) solution of the crude acid chloride in acetone (5 mL). After 20 min the reaction mixture was poured onto ice, extracted with CH_2Cl_2, washed with brine (2×), and dried ($MgSO_4$). The solvent was removed in vacuo to give the acyl azide **81** as an oil (22.8 mg). tlc: R_f 0.47 (Skellysolve B/acetone, 7:3), 0.54 (Skellysolve B/ethyl acetate, 1:1); ir (CH_2cl_2, cast): 2134, 1704, 1179, 1141, 1007, 735, 698 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): spectrum of **81** is identical to the spectrum of the acid **80**.

A solution of the acyl azide **81** in p-xylene (4 mL) was refluxed under argon for 36 h. The reaction mixture was added to a solution of lithium aluminum hydride (11 mg, 0.29 mmol) in dry ethyl ether (3 mL). The mixture was refluxed for 2 h. The hydride present was destroyed with water (Caution: exothermic reaction). 30% NaOH (5 mL) was added, then the mixture refluxed for 1 h and extracted with CH_2Cl_2. The organic layer was washed with brine (2×) and dried ($MgSO_4$). Removal of the solvent yielded an oil (49.2 mg). A solution of the crude product, methyl iodide

(0.1 mL) and potassium carbonate (excess) in ethanol (5 mL) was refluxed for 36 h under argon. The solid was removed by filtration and washed with CH_2Cl_2 several times. The organic extract was evaporated *in vacuo* to give an oil (23.1 mg). Purification by flash chromatography (Skellysolve B/acetone, 87:13) afforded the mixture of olefins **82** as an oil (2.3 mg); tlc: R_f 0.56 (Skellysolve B/acetone, 7:3); ^1H nmr (200 MHz, $CDCl_3$): δ4.67 (br s, H-18), 4.43 (br s, H-18), 0.95 (s, C-10 CH_3), 0.73 (s, C-10 CH_3), 0.65 (s, C-10 CH_3). The last three signals correspond to the angular methyl of each of the isomers. The ratio is *ca.* 1:3:4.25 respectively (determined by ^1H nmr).

(1S,5R,6R,9R,11R,13R)-5-Acetyloxy-11-benzyloxy-1,5-dimethyl-9-ethylenedioxymethyl-10-oxatricyclo-[7,4,0,0^{9,13}]tridecane 83 and mixture of olefins 84

A solution of the acid **80** (α epimer) (99.5 mg, 0.23 mmol), lead tetraacetate (255 mg, 0.575 mmol), and pyridine (0.2 mL) in benzene (5 mL) under an argon atmosphere was stirred at r.t. for 1 1/2 h, then refluxed for 1 h. The excess reagent was destroyed with ethylene glycol (0.05 mL). The mixture was stirred for 1/2 h, then poured onto water and extracted with CH_2Cl_2 (3×). The organic extract was washed with 10% HCl (2×), satd $NaHCO_3$

(2×), brine (×), dried ($MgSO_4$), and the dichloromethane removed under vacuum to give the crude product (84.7 mg) as a yellow oil. The components of the mixture were separated by flash chromatography (Skellysolve B/acetone, 85:15) to the isomeric olefins **84** (14.8 mg, 17%) and the acetate **83** (24.4 mg, 24%) as an oil.

The mixture of olefins **84** presents the following characteristics: tlc: R_f 0.5 (Skellysolve B/acetone, 7:3); ir (CH_2Cl_2, cast): 3050, 3020, 1650, 1142, 1122, 1090, 1073, 1005, 945, 735, 697 cm^{-1}; the ^1H nmr shows that the three olefins are in a ratio of 1:2:2.3. ^1H nmr (360 MHz, $CDCl_3$): δ0.99 (19%, s, C-10 CH_3), 0.78 (37%, s, C-10 CH_3), 0.69 (43%, s, C-10 CH_3); hrms: m/z calcd for $C_{21}H_{27}O_2$ ($M^+ - C_3H_5O_2$): 311.2004; found: 311.2011(20), 219(8), 191(2), 163(1), 121(4), 91(100), 73(15).

The acetate **83** presents the following characteristics: tlc: R_f 0.42 (Skellysolve B/acetone, 7:3), 0.25 (Skellysolve B/ethyl acetate, 7:3); ir (CH_2Cl_2, cast): 1727, 1248, 1140, 1120, 1103, 1065, 946, 735, 695 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ7.35-7.22 (5H, m, Ar-H), 5.27 (1H, d, 6 Hz, H-12), 5.24 (1H, s, H-14), 4.81 (1H, d, 12 Hz, $ArCH_2O$-), 4.47 (1H, d, 12 Hz, $ArCH_2O$-), 4.05-3.78 (4H, m), 2.63 (1H, m), 2.46 (1H, dt, 12.5, 3 Hz, H-7β), 2.37 (1H, ddd, 14, 11, 6 Hz, H-11β), 2.10 (1H, dd, 14 6 Hz, H-11α), 1.93 (3H, s, CH_3COO), 1.75 (1H, dd, 12.5, 2.75

Hz, H-5), 1.41 (3H, s, C-4 CH_3), 2.08-1.13 (9H, m), 0.91 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ170.1 (s, $CH_3\underline{C}OO$), 138.6 (s, Ar), 128.2 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar), 105.4 (d, C-14), 104.5 (d, C-12), 85.2 (s, C-8), 84.2 (s, C-4), 69.3 (t, $Ar\underline{C}H_2O$), 66.1 (t), 64.6 (t), 58.9 (d, C-9), 55.5 (d, C-5), 38.7 (t), 37.9 (t), 37.0 (s, C-10), 35.9 (t), 31.1 (t), 22.7 (q, $\underline{C}H_3COO$), 20.1 (t), 19.4 (t), 18.4 (q), 15.6 (q); hrms: m/z calcd for $C_{23}H_{31}O_4$ ($M^+ - C_3H_5O_2$): 371.2214; found: 371.2222(20), 311(7), 221(30), 203(4), 121(3), 91(100), 73(22).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) on the angular methyl gave the following results: presaturation of C-10 CH_3 (δ0.91), 16% (1.41, C-4 CH_3), 15% (5.24, H-14), 9% (2.37, H-11β).

(1S,5R,6S,9R,11R,13R)-11-Benzyloxy-1,5-dimethyl-5-diphenylcarbinol-9-ethylenedioxymethyl-10-oxatricyclo-[7,4,0,$0^{9,13}$]tridecane 85 and (1S,5R,6S,9R,11S,13R)-11-benzoyloxy-1,5-dimethyl-5-diphenylcarbinol-9-ethylenedioxymethyl-10-oxatricyclo[7,4,0,$0^{9,13}$]tridecane 86

A 2 M solution of phenyllithium/Et_2O (1.26 mL, 2.5 mmol) was added to a solution of the methyl ester 79 (375.3 mg, 0.84 mmol) in Et_2O (5 mL) cooled in a salted ice bath. The reaction mixture was stirred for 30 min at -5° under argon. The reaction was quenched with water

(0.5 mL) and diluted with Et_2O. The organic layer was washed with H_2O (2×), brine (2×), dried ($MgSO_4$), and the solvent removed *in vacuo* to give the alcohols as an oil. Purification of the crude by flash chromatography (Skellysolve B/ethyl acetate, 65:35) yield **85** (33.6 mg) and **86** (381.9 mg) as an oil in 87%.

The alcohol **85** presents the following characteristics: tlc: R_f 0.35 (Skellysolve B/acetone, 7:3), 0.43 (Skellysolve B/ethyl acetate, 65:35); ir (CH_2Cl_2, cast): 3450 (br), 3050, 1600, 1495, 1453, 1147, 1124, 1087, 1067, 1057, 945, 752, 701 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ ~~7.81 (2H, d,~~ 8 Hz, Ar-H), 7.53 (2H, dd, 8, 1.5 Hz, Ar-H), 7.41-7.11 (11H, m), 5.26 (1H, s, H-14), 5.19 (1H, t, 6 Hz, H-12), 4.80 (1H, d, 12 Hz, Ar$\underline{C}$$H_2$O-), 4.49 (1H, d, 12 Hz, Ar$\underline{C}$$H_2$O-), 4.08-3.69 (4H, m), 2.49 (1H, s, D_2O exchangeable), 2.19 (1H, ddd, 14.5, 11, 6 Hz, H-11β), 2.04 (1H, dt, 12.5, 3 Hz, H-7β), 1.96-0.79 (11H, m), 1.24 (3H, s), 1.06 (3H, s), 0.64 (1H, td, 12.5, 4 Hz); ^{13}C nmr ($CDCl_3$): δ145.7 (s), 145.3 (s), 138.4 (s), 128.4 (d), 128.3 (d, 3×), 127.8 (d, 2×), 127.5 (d, 4×), 127.3 (d), 127.2 (d, 2×), 126.6 (d), 126.5 (d), 105.3 (d, C-14), 105.0 (d, C-12), 84.1 (s, C-8), 82.1 (s, C-18), 70.6 (t), 65.8 (t), 65.0 (t), 61.7 (d, C-9), 51.7 (d, C-5), 46.4 (s, C-4), 39.2 (t), 37.7 (t), 37.0 (s, C-10), 35.8 (t), 30.1 (t), 22.2 (t), 18.5 (t, C-2), 16.3 (q), 15.8 (q); hrms:

m/z calcd for $C_{34}H_{39}O_3$ (M^+ - $C_3H_5O_2$): 495.2889; found: 495.2899(20), 313(6), 277(3), 221(6), 183(19), 121(2), 105(34), 91(100), 73(26).

The alcohol **86** presents the following properties: tlc: R_f 0.35 (Skellysolve B/acetone, 7:3), 0.35 (Skellysolve B/ethyl acetate, 65:35); ir (CH_2Cl_2, cast): 3460 (br), 3055, 1590, 1491, 1445, 1140, 1121, 1091, 1059, 1027, 1003, 942, 751, 702 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.81 (2H, d, 7.5 Hz, Ar-H), 7.53 (2H, d, 7.5 Hz, Ar-H), 7.38-7.14 (11H, m), 5.19 (1H, d, 6 Hz, H-12), 5.15 (1H, s, H-14), 4.75 (1H, d, 12 Hz, $ArCH_2O$-), 4.42 (1H, d, 12 Hz, $Ar\underline{C}H_2O$), 3.98-3.71 (4H, m), 2.44 (1H, s, D_2O exchangeable), 2.28 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.08 (1H, dt, 12.5, 3 Hz, H-7β), 1.96 (1H, td, 13, 4 Hz), 1.91-1.80 (3H, m), 1.67-1.1 (6H, m), 1.18 (3H, s), 0.94 (3H, s), 0.86-0.76 (2H, m); ^{13}C nmr ($CDCl_3$): δ145.9 (s), 145.7 (s), 128.3 (d), 128.2 (d, 2×), 127.9 (d, 2×), 127.8 (d, ×), 127.6 (d, 2×), 127.3 (d, ×), 127.3 (d, 3×), 126.6 (d), 126.5 (d), 105.6 (d, C-14), 104.5 (d, C-12), 84.2 (s, C-8), 84.0 (s, C-18), 69.3 (t), 65.9 (t), 64.6 (t), 59.6 (d, C-9), 51.8 (d, C-5), 46.7 (s, C-4), 39.5 (t), 37.8 (t), 37.4 (s, C-10), 36.0 (t), 31.5 (t), 22.4 (t), 18.6 (t, C-2), 16.5 (q), 16.2 (q); hrms: m/z calcd for $C_{34}H_{39}O_3$ (M^+ - $C_3H_5O_2$): 495.2889; found: 495.2899(20), 313(3), 278(6), 235(9), 221(7), 183(31), 155(5), 115(29), 105(35), 91(100), 73(46); cims (NH_3): 478(11), 461(100), 443(7).

Formation of the mixture **84** from **85**

A mixture of the alcohol **85** (381.9 mg, 0.67 mmol), lead tetraacetate (327.4 mg, 0.74 mmol), and $CaCO_3$ (200 mg, 1.99 mmol) in dry benzene (6 mL) was vigorously stirred at 40°C under argon. The reaction was quenched with ethylene glycol after 30 min. The reaction mixture was diluted with Et_2O, then placed under argon for 2 h. The suspension was filtered, then Et_2O was added to the solid and the mixture refluxed for 30 min. The suspension was filtered and the last step repeated once more. The ethereal extracts were combined, washed with satd $NaHCO_3$ (2×), brine (2×), dried ($MgSO_4$), and the ether removed under vacuum to yield a solid. Purification of the crude product by flash chromatography (dichloromethane/acetone, 98:2) gave the isomeric olefins **84** (197.8 mg, 77%) as an oil. The ^1H nmr shows that the mixture is formed of the olefins $\Delta^{4,(18)}$ (δ0.68, 85%), Δ^3 (δ0.76, 11%), and Δ^4 (δ0.98, 4%). A pure sample of the exocyclic olefin **23** was obtained from the photoxygenation of the mixture as an oil: tlc: R_f 0.51 (Skellysolve B/acetone, 7:3), 0.33 (dichloromethane/acetone, 98:2); $[\alpha]_D$ -27° (c 0.29 $CHCl_3$); ir (CH_2Cl_2, cast): 3070, 3030, 1650, 1453, 1118, 1004,

943, 886, 734, 697 cm^{-1}; ^{1}H nmr (400 MHz, CDCl$_3$): δ7.35-7.22 (5H, m, Ar-H), 5.28 (1H, d, 6 Hz, H-12), 5.22 (1H, s), 4.82 (1H, d, 12 Hz, ArCH$_2$O-), 4.70 (1H, d, 1.5 Hz, C=CH$_2$), 4.49 (1H, d, 12 Hz, ArCH$_2$O-), 4.44 (1H, d, 1.5 Hz, C=CH$_2$), 4.04-3.77 (4H, m), 2.44 (1H, dd, 9, 3 Hz, H-5), 2.35 (1H, ddd, 14.5, 11, 6 Hz, H-11β), 2.27 (1H, dt, 13, 3 Hz), 2.14 (1H, dd, 14.5, 7 Hz, H-11α), 2.0 (1H, m), 1.88 (1H, br d, 10 Hz), 1.69 (1H, dd, 11.5, 7 Hz, H-9), 1.72-1.49 (7H, m), 1.33 (1H, td, 12, 7 Hz), 0.7 (3H, s, C-10 CH$_3$); ^{13}C nmr (CDCl$_3$): δ149.2 (s, C-4), 138.6 (s, Ar), 128.2 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.3 (d, Ar), 105.2 (d, C-14), 105.0 (t, C-18), 104.6 (d, C-12), 84.3 (s, C-8), 69.4 (t, ArCH$_2$O-), 66.0 (t), 64.6 (t), 57.6 (d, C-9), 53.0 (d, C-5), 39.5 (t), 38.1 (t), 36.4 (t), 35.5 (s), 31.6 (t), 23.3 (t), 22.9 (t), 13.3 (q, C-20); hrms: m/z calcd for $C_{21}H_{27}O_2$ ($M^+ - C_3H_5O_2$): 311.2004; found: 311.2011(28), 219(8), 191(2), 121(2), 91(100), 73(15); cims (NH$_3$): 311(6), 294(46), 277(86), 91(44).

Analysis: Calcd for $C_{24}H_{32}O_4$: C 74.96, H 8.38; Found: C 74.82, H 8.40.

(1S,5R,6R,9R,11R,13R)-11-Benzoyloxy-9-ethylenedioxymethyl-1-methyl-10-oxa-5-oxaspirotricyclo[7,4,0,$0^{9,13}$]tridecane

87

A solution of m-chloroperbenzoic acid (69.4 mg, 0.4

mmol) in CH_2Cl_2 (4 mL) was added to a solution of the mixture of olefins **84** (128.9 mg, 0.335 mmol) in CH_2Cl_2 (8 mL) cooled in an ice bath. The solution was stirred at r.t. for 3 h, then methyl sulfide (0.02 mL) was added. The reaction mixture was diluted with CH_2Cl_2, washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to yield a mixture of epoxides (130 mg, 97%) as a colorless oil. Purification of the epoxides by flash chromatography (Skellysolve B/acetone, 3:1) afforded a pure sample of **87**. tlc: R_f 0.36 (Skellysolve B/acetone, 7:3), 0.36 (dichloromethane/acetone, 95:5); ir (CH_2Cl_2, cast): 3030, 1453, 1114, 1075, 1004, 942, 818, 735, 698 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 7.4-7.21 (5H, m, Ar-H), 5.29 (1H, d, 6 Hz, H-12), 5.20 (1H, s, H-14), 4.83 (1H, d, 12 Hz, $ArCH_2O$-), 4.49 (1H, d, 12 Hz, $ArCH_2O$-), 4.07-3.76 (4H, m), 2.74 (1H, dd, 4.5, 1.5, Hz, H-18), 2.57 (1H, d, 4.5 Hz, H-18), 2.46-2.32 (2H, m). 2.12 (1H, dd, 14.5, 6.5 Hz, H-11α), 1.92 (1H, m, H-3α), 1.69 (1H, dd, 11.5, 6.5 Hz, H-9), 1.82-0.94 (9H, m), 0.94 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{21}H_{27}O_3$ ($M^+ - C_3H_5O_2$): 327.1953; found: 327.1960(28), 235(3), 219(3), 115(2), 91(100), 73(22).

(1S,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-5-hydroxymethyl-1-methyl-10-oxatricyclo[7,4,0,$0^{9,13}$]tridec-4-ene **88**

A 2.7 M solution of ethyl magnesium bromide/Et_2O (0.8 mL, 2.16 mmol) was added slowly to a solution of isopropylcyclohexylamine (0.39 mL, 2.4 mmol) in THF (4 mL) cooled in an ice bath. The solution was refluxed for 45 min after addition was complete, then cooled to room temperature. The epoxide **87** (96.2 mg, 0.24 mmol) in 1 mL of THF was added to the amine solution then the flask placed in an oil bath at 40°C for 28 h. The reaction was quenched with 10% NH_4Cl (4 mL) and diluted with CH_2Cl_2. The reaction mixture was washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a yellow oil (96.3 mg). The crude product was purified by flash chromatography (dichloromethane/acetone, 85:15) to obtain the secondary alcohol **95** (12 mg) and the primary alcohol **88** (18.8 mg, 20%) as an oil.

The primary alcohol presents the following properties: tlc: R_f 0.23 (Skellysolve B/acetone, 7:3), 0.32 (dichloromethane/acetone, 85:15); ir (CH_2Cl_2, cast): 3450, 3030, 1450, 1120, 1005, 942, 735, 695 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 7.35-7.22 (5H, m, Ar-H), 5.60 (1H, m, H-3), 5.29 (1H, d, 6 Hz, H-12), 5.26 (1H, s, H-14), 4.83 (1H, d, 12 Hz, $ArCH_2O$-), 4.50 (1H, d, 12 Hz, $ArCH_2O$-), 4.12-3.92 (4H, m), 3.88-3.78 (2H, m), 2.49 (1H, dt, 12, 3 Hz, H-7β), 2.43 (1H, ddd, 14, 11, 6 Hz, H-11β), 2.24 (1H, m), 2.17 (2H, m), 2.09 (1H, dd, 14, 6.5 Hz, H-11α), 2.13-2.06 (1H, m), 1.73 (1H, dd, 11.5, 7 Hz, H-9), 1.63-1.41 (4H, m), 1.15 (1H, t, 6 Hz, D_2O exchangeable), 0.81 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ138.7 (s, Ar), 137.3 (s, C-4), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar, 1×), 124.3 (d, C-3), 105.5 (d, C-14), 104.6 (d, C-12), 84.4 (s, C-8), 69.4 (t), 66.0 (t), 65.4 (t, C-18), 64.6 (t), 56.8 (d, C-9), 47.8 (d, C-5), 36.0 (t), 35.8 (t), 34.9 (s, C-10), 31.6 (t), 22.6 (t), 22.2 (t), 12.6 (q); hrms: m/z calcd for $C_{21}H_{27}O_3$ ($M^+ - C_3H_5O_2$): 327.1953; found: 327.1972(25), 235(2), 219(4), 189(82), 119(5), 91(100), 73(18).

(1S,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-1-methyl-10-oxa-5-(tert-butyl)dimethylsilyloxymethyltricyclo[7,4,0,$0^{9,13}$]tridec-4-ene **89**

A solution of the crude alcohols **88** (87.3 mg), diisopropylethylamine (0.06 mL, 0.344 mmol) in THF (2 mL) was cooled in an ice bath. t-Butyldimethylchlorosilane (39.4 mg, 0.26 mmol) was added to the solution, then stirred at room temperature for 1 h. The reaction was quenched with H_2O (0.06 mL), stirred for 10 min, and diluted with Et_2O. The organic solution was washed with satd $NaHCO_3$ (2×), H_2O (3×), brine (2×), dried ($MgSO_4$), and the solvent removed to yield an oil (83.1 mg). Purification by flash chromatography (Skellysolve B/acetone, 9:1) gave the primary protected alcohol (23 mg, 20% overall yield from the epoxide) and the secondary alcohol (10 mg), each as a colorless oil.

The primary protected alcohol **89** presents the following properties: tlc: R_f 0.55 (dichloromethane/acetone, 95:5), 0.45 (Skellysolve B/acetone, 4:1); ir (CH_2Cl_2, cast): 3035, 1255, 1124, 1093, 1060, 944, 836, 775 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.36-7.22 (5H, m, Ar-H), 5.55 (1H, m, H-3), 5.3 (1H, d, 6 Hz, H-12), 5.25 (1H, s, H-14), 4.84 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.51 (1H, d, 12 Hz, $ArCH_2O$-), 4.11 (1H, d, 13.5 Hz, H-18), 4.04-3.94 (3H, m), 3.88-3.8 (2H, m), 2.46 (1H, dt, 12, 3 Hz, H-7β), 2.43 (1H, ddd, 14, 11.5, 6 Hz, H-11β), 2.24-2.12 (2H, m), 2.08 (1H, dd, 14.5, 7 Hz, H-11α), 2.04 (1H, dd, 10.5, 7.5 Hz, H-5), 1.73 (1H, dd, 11.5, 7 Hz, H-9), 1.64-1.41 (5H, m), 0.93 (9H, s, $-C(CH_3)_3$), 0.82 (3H, s, C-10 CH_3), 0.08 (6H, s, Si-CH_3); hrms: m/z calcd for $C_{27}H_{41}O_3Si$ ($M^+ - C_3H_5O_2$): 441.2814; found: 441.2825(70), 311(10), 217(14), 189(7), 115(11), 91(100), 73(26).

(1S,4R,5R,6R,9R,11R,13R)-11-Benzyloxy-4,5-epoxy-9-ethylenedioxymethyl-1-methyl-10-oxa-5-(*tert*-butyl)-dimethylsilyloxymethyltricyclo[7,4,0,$0^{9,13}$]tridecane **90**

A solution of *m*-chloroperbenzoic acid (7.3 mg) in CH_2Cl_2 (2 mL) was added to a cooled (ice bath) solution of the olefin **89** (14.6 mg, 0.028 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature for 3 h. Methyl sulfide (0.04 mL) was added to the solution then stirred for 10 min. The reaction mixture was diluted with CH_2Cl_2, washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and concentrated to give the epoxide **90** (13.3 mg, 89%) as an oil. tlc: R_f 0.37 (Skellysolve B/ethyl acetate, 7:3), 0.41 (Skellysolve B/acetone, 4:1); ir (CH_2Cl_2, cast): 3030, 1253, 1140, 1121, 1092, 1075, 942, 837, 778, 695 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ7.35-7.21 (5H, m, Ar-H), 5.26 (1H, d, 6 Hz, H-12), 5.24 (1H, s, H-14), 4.82 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.47 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 3.9 (1H, d, 11 Hz, H-18), 4.04-3.78 (4H, m), 3.4 (1H, d, 11 Hz, H-18), 3.11 (1H, d, 3 Hz, H-3), 2.46 (1H, dt, 12, 3 Hz, H-7β), 2.34 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.11-2.01 (2H, m), 1.93 (1H, dd, 14, 7 Hz, H-11α), 2.0-1.90 (1H, m), 1.79-1.09 (6H, m), 0.89 (9H, s, $-C(CH_3)_3$), 0.86 (3H, s, C-10 CH_3), 0.05 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3)); ^{13}C nmr ($CDCl_3$): δ138.5 (s, Ar), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.5 (d, Ar), 105.3

(d, C-14), 104.4 (d, C-12), 83.9 (s, C-8), 69.4 (t), 66.1 (t), 64.7* (t, C-18), 64.6* (t), 59.2 (s, C-4), 56.4# (d, C-9), 56.3# (d, C-3), 51.0 (d, C-5), 35.9 (t), 34.3 (s, C-10), 33.9 (t), 31.8 (t), 25.9 (q, 3×), 21.5 (t), 20.6 (t), 18.3 (s), 13.0 (q, C-20); hrms: m/z calcd for $C_{26}H_{37}O_6Si$ ($M^+ - C_4H_9$): 473.2349; found: 473.2360(4), 457(21), 219(3), 91(100), 73(33).

(1S,4R,5R,6R,9R,11R,13R)-11-Benzyloxy-4,5-epoxy-9-ethylenedioxymethyl-5-hydroxymethyl-1-methyl-10-oxatricyclo[7,4,0,$0^{9,13}$]tridecane 91

A solution of m-chloroperbenzoic acid (12.2 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was added to the allylic alcohol **88** (18.8 mg, 0.047 mmol) in CH_2Cl_2 (3 mL) cooled in an ice bath. The reaction mixture stirred at room temperature for 1 h. Methyl sulfide (0.02 mL) was added and the solution stirred for 10 min, then diluted with CH_2Cl_2, washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated to yield the epoxide **91** (15.2 mg, 77%) as a colorless oil. tlc: R_f 0.26 (Skellysolve B/acetone, 3:2), 0.19 (dichloromethane/acetone, 85:15); ir (CH_2Cl_2, cast): 3457 (br), 1453, 1121, 1109, 1075, 1038, 1006, 942, 735, 698 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.3-7.22 (5H, m, Ar-H), 5.26 (1H, d, 6 Hz, H-12), 5.24 (1H, s, H-14), 4.8 (1H, d, 12 Hz, $ArCH_2O$-), 4.47 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.02-3.78 (5H, m), 3.58 (1H, d, 12.5 Hz, H-18), 3.31 (1H, d, 3.5 Hz, H-3), 2.45 (1H, m, H-7β), 2.35 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.08 (1H, dd, 9, 4 Hz, H-5), 2.07 (1H, dd, 16, 7 Hz, H- 2α), 1.93 (1H, dddd, 16, 13, 7.5, 3.5 Hz, H-2β), 1.91 (1H, dd, 14.5, 7 Hz, H-11α), 1.72 (1H, br, D_2O exchangeable), 1.63 (1H, dd, 11.5, 7 Hz, H-9), 1.67-1.61 (1H, m), 1.57-1.45 (2H, m), 1.40 (1H, dd, 13.5, 7.5 Hz, H-1β), 1.17 (1H, dd, 13, 7 Hz, H-1α), 0.85 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ138.3 (s, Ar), 128.7 (d, Ar, 2×), 127.7 (d, Ar, 2×), 127.4 (d, Ar), 105.0 (d, C-14), 104.3 (d, C-12), 83.5 (s, C-8), 69.4 (t), 66.1 (t), 64.6 (t), 61.5 (t, C-18), 59.8 (s, C-4), 56.1* (d, C-9), 55.0* (d, C-3), 50.3 (d, C-5), 35.7 (t), 34.3 (s, C-10), 33.5 (t), 31.6 (t), 21.2 (t), 20.3 (t), 17.6 (q, C-20); hrms: m/z calcd for $C_{21}H_{27}O_4$ ($M^+ - C_3H_5O_2$): 343.1902; found: 343.1909(12), 325(5), 251(2), 233(2), 91(100), 73(15).

(1S,4R,5S,6S,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-4-hydroxy-5-(1-hydroxyethyl)-1-methyl-10-oxatricyclo[7,4,0,0^{9,13}]tridecane 92

In a dry flask was placed CuI (56.7 mg, 0.29 mmol) in Et_2O (1 mL) then the flask cooled to -40°C in a dry ice/acetonitrile bath under an argon atmosphere. A 1.2 $\underline{M}$ solution of methyllithium/Et_2O (0.54 mL, 0.65 mmol) was added to the mixture and the temperature was brought slowly to 0°C. The epoxide **91** (12.4 mg, 0.03 mmol) in Et_2O (0.5 mL) was added to the cuprate reagent. The slurry was stirred at 0°C for 1 h, warmed to room temperature, then THF (0.3 mL) added and stirred for 10 h. The reaction was quenched with 10% NH_4Cl (1 mL) and diluted with Et_2O. The organic layer was washed with H_2O (2×), brine (2×), dried ($MgSO_4$), and concentrated _in vacuo_ to give an oil (5.2 mg). Purification by flash chromatography (ethyl acetate/Skellysolve B, 4:1) gave two epimeric alcohols **92** (0.9 mg and 0.7 mg) each as a solid.

The alcohol **92b** presents the following characteristics: tlc: R_f 0.29 (ethyl acetate/Skellysolve B, 3:1), 0.3 (Skellysolve B/acetone, 3:2), 0.26 (dichloromethane/methanol, 96:4); ir (CH_2Cl_2, cast): 3400 (br), 1120, 1057, 1005, 948, 730, 695 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.28 (5H, m, Ar-H), 5.29 (1H, d, 6 Hz, H-12), 5.21 (1H, s, H-14), 4.83 (1H, d, 12 Hz, ArCHCH_2O-), 4.47 (1H, d, 12 Hz, ArCH_2O-), 4.39 (1H, br s, H-3), 4.08 (1H, td, 6.5, 2.5 Hz), 4.04-3.91 (2H, m), 3.87-3.79 (2H, m), 2.6 (1H, d, 6.5 Hz, D_2O exchangeable), 2.53 (1H, d, 1.5 Hz, D_2O exchangeable), 2.45 (1H, dt, 12.5, 2.5 Hz, H-7β), 2.37 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.18 (1H, dd, 14.5, 6.5 Hz, H-11α), 2.01 (1H, td, 12, 3.5 Hz, H-5), 2.03-1.95 (1H, m), 1.78 (1H, m), 1.70 (1H, dd, 11, 6.5 Hz, H-9), 1.67-1.13 (6H, m), 1.31 (3H, d, 6.5 Hz), 0.83 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{22}H_{31}O_4$ (M^+ - $C_3H_5O_2$): 359.2214; found: 359.2222(9), 327(1), 233(1), 119(1), 91(100), 73(20).

The alcohol **92a** presents the following properties: tlc: R_f 0.22 (ethyl acetate/Skellysolve B, 3:1), 0.25 (Skellysolve B/acetone, 3:2), 0.21 (dichloromethane/methanol, 96:6); ir (CH_2Cl_2, cast): 3440, 1121, 1090, 1067, 1007, 948, 735, 697 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.28 (5H, m, Ar-H), 5.27 (1H, d, 6 Hz, H-12), 5.23 (1H, s, H-14), 4.82 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.48 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.10-4.04 (2H, m, H-3, H-18), 4.04-3.91 (2H, m), 3.88-3.78 (2H, m), 2.49 (1H, d, 2 Hz, D_2O exchangeable), 2.43 (1H, dt, 12, 3 Hz, H-7β), 2.36 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.12 (1H, dd, 14.5, 7 Hz, H-11α), 2.15-2.08 (1H, m), 1.94 (1H, td, 12, 3.5 Hz, H-5), 1.85 (1H, m), 1.73 (1H, d, 3 Hz, D_2O exchangeable), 1.69 (1H, dd, 11.5, 6.5 Hz, H-9), 1.36 (1H, dt, 12, 2 Hz, H-4), 1.65-1.19 (5H, m), 1.30 (3H, d, 7 Hz), 0.86 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{22}H_{31}O_4$ (M^+ - $C_3H_5O_2$): 359.2214; found: 359.2222(16), 251(2), 231(2), 189(1), 107(2), 91(100), 73(19).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) of the angular methyl gave the following results: presaturation of C-10 CH_3 (δ0.86) gave a 9% (δ5.27, H-14) and 11% (δ1.36, H-4) enhancement on those signals.

(1S,4R,6S,9R,11R,13R)-9-Ethylenedioxymethyl-11-ethoxy-4-hydroxy-1-methyl-5-methylene-10-oxatricyclo[7,4,0,$0^{9,13}$]-tridecane **93**

A solution of the mixture of olefins **84** (59 mg, 0.153 mmol), selenium dioxide (8.5 mg, 0.076 mmol), and 2 drops of H_2O in absolute ethanol (8 mL) was refluxed for 7 h under an inert atmosphere (Ar). The solution was filtered to remove the metallic selenium and evaporated to give a yellow oil. The crude product was purified by flash chromatography (ethyl acetate/Skellysolve B, 7:3) to obtain the starting material (10 mg) and the allylic alcohol **93** (18.6 mg, 36%), each fraction as an oil. tlc: R_f 0.32 (Skellysolve B/acetone, 7:3), 0.34 (ethyl acetate/Skellysolve B, 3:7), 0.32 (dichloromethane/methanol, 95:5); ir (CH_2Cl_2, cast): 3453, 3075, 1655, 1118, 1058, 975, 870, 800, 740 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ5.2 (1H, s, H-14), 5.19 (1H, d, 5.5 Hz, H-12), 4.94 (1H, t, 1.5 Hz, H-18), 4.60 (1H, t, 1.5 Hz, H-18), 4.27 (1H, t, 2.5 Hz, H-3), 4.03-3.91 (2H, m), 3.85-3.75 (3H, m), 3.43 (1H, dq, 9.5, 7 Hz, OCH_2CH_3), 2.50 (1H, br d, 12 Hz, H-7β), 2.42 (1H, complex, H-5), 2.32 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.16 (1H, dd, 14, 7.5 Hz, H-11α), 1.87-1.69 (3H, m), 1.64-1.46 (4H, m), 1.37 (1H, s, D_2O exchangeable), 1.35 (1H, m), 1.17 (3H, t, 7 Hz, OCH_2CH_3), 0.69 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ150.7 (s, C-4), 108.5 (t, C-18), 105.3 (d, C-14), 105.0 (d, C-12), 83.9 (s, C-8), 73.2 (d, C-3), 66.0 (t), 64.6 (t), 63.0 (t), 57.4 (d, C-9), 46.5 (d, C-5), 38.2 (s, C-10), 35.5 (t), 34.1 (t), 31.6 (t), 29.6 (t), 22.9 (t), 15.3 (q), 12.5 (q); hrms: m/z calcd for $C_{19}H_{29}O_5$ (M^+ - 1): 337.2007; found: 337.2014(0.5), 293(3), 265(100), 219(4), 201(10), 157(7), 119(9), 91(14), 73(29).

(1S,6S,9R,11R,13R)-9-Ethylenedioxymethyl-11-ethoxy-methyl-5-methylene-10-oxatricyclo[7,4,0,$0^{9,13}$]tridec-2-ene **94**

Mesyl chloride (0.15 mL) was added to a solution of the allylic alcohol **93** (9 mg, 0.026 mmol) and triethylamine (0.1 mL) in 2 mL of dry CH_2Cl_2 cooled in an ice bath. The reaction mixture was stirred at 5°C for 30 min and at room temperature for 1 h. The mixture was poured onto ice-water, then extracted with CH_2Cl_2 (2×). The combined extract was washed with 10% HCl (2×), satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and evaporated *in vacuo* to give an oil (20 mg). Purification by flash chromatography (Skellysolve B/acetone, 85:15) gave **93** as a colorless oil (1 mg). tlc: R_f 0.20 (Skellysolve B/acetone, 4:1), 0.43 (dichloromethane/acetone, 95:5), 0.26 (Skellysolve B/ethyl acetate, 3:1); ir (CH_2Cl_2, cast): 3020, 1635, 1595, 1181, 1118, 1080, 1040, 953, 935, 882, 870 cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ6.2 (1H, dd, 10, 2.5 Hz, H-3), 5.61 (1H, m, H-2), 5.2 (1H, d, 6 Hz, H-12), 5.18 (1H, s, H-14), 4.83 (1H, br s, H-18), 4.75 (1H, br s, H-18), 4.03-3.89 (2H, m), 3.85-3.72 (3H, m), 3.42 (1H, dq, 9.5, 7 Hz, $O\underline{CH_2}CH_3$), 2.40 (1H, dt, 12, 3.5 Hz, H-7β), 2.35 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.15-2.04 (2H, m), 2.05 (1H, dd, 14.5, 7 Hz, H-11α), 1.95 (1H, dd, 18, 5.75 Hz), 1.94-1.86 (1H, m), 1.55 (1H, dd, 11.5, 7 Hz, H-9), 1.6-1.38 (2H, m), 1.14 (3H, t, 7 Hz, $OCH_2\underline{CH_3}$), 0.68 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{19}H_{27}O_4$ (M^+ - 1): 319.1902; found: 319.1910(3), 275(16), 247(100), 201(20), 133(10), 157(16), 149(9), 119(22), 105(17), 91(18), 73(40).

(1S,4R,6S,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-4-hydroxy-1-methyl-5-methylene-10-oxatricyclo-[7,4,0,$0^{9,13}$]tridecane 95

Selenium dioxide (6 mg, 0.054 mmol) was added to CH_2Cl_2 (2 mL) followed by a 90% solution of *t*-butylhydroperoxide (0.23 mL, 2.08 mmol) and the mixture was stirred for 30 min. The mixture of olefins **84** (195.3 mg, 0.508 mmol) in CH_2Cl_2 (3 mL) was added to the oxidizing reagents and stirred at room temperature for 5

h. The reaction was cooled in an ice bath and trimethylphosphite (0.24 mL, 2.08 mmol) added carefully. The solution was diluted with benzene, then concentrated in vacuo to give a yellow oil. Purification by flash chromatography (Skellysolve B/ethyl acetate, 1:1) afforded the starting material (28.7 mg) and the allylic alcohol **95** (95.7 mg, 47%), each as a colorless oil.

The allylic alcohol **95** has the following characteristics: tlc: R_f 0.3 (Skellysolve B/acetone, 7:3), 0.3 (Skellysolve B/ethyl acetate, 1:1); $[\alpha]_D$ -39.0 (c 0.385, $CHCl_3$); ir (CH_2Cl_2, cast): 3457 (br), 3030, 1655, 1141, 1120, 1058, 1006, 948, 937, 735, 698 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.37-7.20 (5H, m, Ar-H), 5.28 (1H, d, 6 Hz, H-12), 5.22 (1H, s, H-14), 4.93 (1H, br s, H-18), 4.82 (1H, d, 12 Hz, ArCH_2O-), 4.60 (1H, t, 1.5 Hz, H-18), 4.48 (1H, d, 12 Hz, ArCH_2O-), 4.27 (1H, t, 2.5 Hz, H-3), 4.04-3.76 (4H, m), 2.49 (1H, br d, 12 Hz, H-7β), 2.45 (1H, complex, H-5), 2.35 (1H, ddd, 14.5, 11, 6 Hz, H-11β), 2.22 (1H, dd, 14.5, 6.5 Hz, H-11α), 1.68 (1H, dd, 11, 6.5 Hz, H-9), 1.89-1.46 (6H, m), 1.37 (1H, br s, D_2O exchangeable), 1.34 (1H, m), 0.69 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ150.6 (s, C-4), 138.6 (s, Ar), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar), 108.6 (t, C-18), 105.2 (d, C-14), 104.6 (d, C-12), 84.3 (s, C-8), 73.0 (d, C-3), 69.3 (t), 66.1 (t), 64.6 (t), 57.4 (d, C-9), 46.5 (d, C-5), 38.2, 35.5, 34.2, 31.6 (t), 29.5 (t), 23.0 (t), 12.5 (q, C-20); hrms: m/z calcd for $C_{21}H_{27}O_3$ ($M^+ - C_3H_5O_2$): 327.1953; found: 327.1960(22), 309(1), 235(1), 219(9), 119(4), 91(100), 73(18).

Nuclear Overhauser enhancement difference spectroscope (nOeds) of the exocyclic olefinic protons gave the following result: presaturation of the broad singlet at δ4.93: 27% (δ4.6, H-18), 12% (δ4.27, H-3).

(1S,4S,5S,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-4-hydroxy-1-methyl-10-oxa-5-oxaspirotricyclo[7,4,0,$0^{9,13}$]tridecane **96**

A solution of m-chloroperbenzoic acid (368.5 mg, 2.13 mmol) in CH_2Cl_2 (6 mL) was added to a solution of the allylic alcohol **95** (427.6 mg, 1.06 mmol) in CH_2Cl_2 (6 mL) cooled in an ice bath. The reaction mixture was stirred at room temperature for 2 h, then methyl sulfide was added (0.1 mL). The solution was washed with satd $NaHCO_3$ (2×), brine (×), dried ($MgSO_4$), and the solvent evaporated to give the epoxide **95** (421.9 mg, 95%) as an oil. tlc: R_f 0.31 (Skellysolve B/acetone, 7:3), 0.31 (ethyl acetate/Skellysolve B, 7:3), 0.38 (dichloromethane/methanol, 96:4); ir (CH_2Cl_2, cast): 3460 (br), 3020, 1450, 1120, 1104, 1064, 1028, 1006, 948, 732, 697 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.21 (5H, m, Ar-H), 5.28 (1H, d, 6 Hz, H-12), 5.1 (1H, s, H-14), 4.82 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.47 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.03-3.89 (2H, m), 3.81-3.75 (2H, m), 3.36 (1H, t, 3 Hz, H-3), 2.85 (1H, d, 4 Hz, H-18), 2.63 (1H, d, 4 Hz, H-18), 2.42-2.30 (3H, m), 2.17 (1H, dd, 14, 7 Hz, H-11α), 1.95 (1H, s, D_2O exchangeable), 1.92-1.79 (2H, m), 1.72-0.95 (6H, m), 0.85 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ138.4 (s, Ar), 128.3 (d, Ar, 2×), 127.7 (d, Ar, 2×), 127.4 (d, Ar), 105.2 (d, C-14), 104.5 (d, C-12), 84.1 (s, C-8), 72.8 (d, C-3), 69.3 (t), 66.1 (t), 64.6 (t), 61.7 (s, C-4), 57.5 (d, C-9), 50.0 (t, C-18), 42.8 (d, C-5), 38.2 (s, C-10), 35.1 (t), 33.2 (t), 31.2 (t), 27.3 (t), 18.6 (t), 13.1 (q, C-20); hrms: m/z calcd for $C_{21}H_{27}O_4$ ($M^+ - C_3H_5O_2$): 343.1902; found: 343.1909(6), 325(1), 251(1), 91(100), 73(18).

(1S,5R,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-1-methyl-10-oxa-5-oxaspiro-4-oxotricyclo[7,4,0,$0^{9,13}$]tridecane **97**

A 2.82 M solution of DMSO/CH_2Cl_2 (0.89 mL, 2.52 mmol) was added to a solution of oxalyl chloride (0.11 mL, 1.32 mmol) in CH_2Cl_2 (2 mL) cooled to -60° in a dry ice/acetone bath and stirred for 5 min. A solution of the alcohol **96** (421 mg, 1.01 mmol) in CH_2Cl_2 (4 mL) was added to the reaction then stirred at -60°C for 15 min. Triethylamine (0.70 mL, 5.05 mmol) was added, the bath removed and the mixture allowed to reach room temperature. The reaction mixture was quenched with H_2O (0.1 mL), diluted with CH_2Cl_2, washed with H_2O (2×), brine (×), dried ($MgSO_4$), and concentrated to afford the ketone **97** (411.2 mg, 98%) as an oil. tlc: R_f 0.39 (dichloromethane/acetone, 9:1), 0.32 (ethyl acetate/Skellysolve B, 7:3); ir (CH_2Cl_2, cast): 1720, 1453, 1142, 1119, 1103, 1084, 940, 736, 698 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.39-7.25 (5H, m, Ar-H), 5.31 (1H, d, 6 Hz, H-12), 5.22 (1H, s, H-14), 4.82 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.48 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.06-3.79 (4H, m), 2.91 (1H, d, 6 Hz, H-18), 2.70 (1H, d, 6 Hz, H-18), 2.67-2.51 (2H, complex), 2.46 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.41 (1H, dt, 12.5, 3 Hz, H-7β), 2.19 (1H, dd, 12.5, 3.5, H-5), 2.14 (1H, dd, 14.5, 7 Hz, H-11α), 1.90 (1H, ddd, 13, 6.5 2 Hz), 1.71 (1H, dd, 11.5, 7 Hz, H-9), 1.78-1.61 (2H, m), 1.5 (1H, td, 13, 4 Hz), 1.16 (1H, dq, 13.5, 3.5 Hz), 1.06 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ205.7 (s, C-3), 138.2 (s, Ar), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.5 (d, Ar), 104.9 (d, C-14), 104.3 (d, C-12), 83.9 (s, C-8), 69.5 (t), 66.2 (t), 64.7 (t), 60.6 (s, C-4), 57.4 (d, C-9), 49.8 (t, C-18), 47.9 (d, C-5), 37.3 (s, C-10), 37.3 (t), 36.9 (t), 34.6 (t), 31.3 (t), 19.2 (t), 13.2 (q, C-20); hrms: m/z calcd for $C_{21}H_{25}O_4$ ($M^+ - C_3H_5O_2$): 341.1746; found: 341.1753(13), 325(1), 249(1), 91(100), 73(19).

(1S,5R,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-1-methyl-4-methylene-10-oxa-5-oxaspirotricyclo-[7,4,0,$0^{9,13}$]tridecane 98

A 35% potassium hydride emulsion (227 mg, 1.98 mmol) was rinsed with Skellysolve B (2×) and benzene (×). Benzene (8 mL) was added to the white solid, followed by tert-amyl alcohol (0.22 mL, 1.98 mmol) and the slurry stirred for 20 min. Triphenylmethylphosphonium bromide (708.7 mg, 1.98 mmol) was added to the solution and the mixture stirred for 15 min. The ketone **97** (411.2 mg, 0.99 mmol) in benzene (7 mL) was added to the slurry and the mixture stirred at room temperature for 2 h. Benzene was added, the reddish yellow solution was washed with H_2O (2×), brine (×), dried ($MgSO_4$), and the solvent was removed *in vacuo* to obtain a red oil. The crude was purified by flash chromatography (dichloromethane/acetone, 97:3) to afford the exocyclic olefin **98** (248.7 mg, 61%) as a colorless oil. tlc: R_f 0.4 (dichloromethane/acetone, 96:4), 0.38 (Skellysolve B/acetone, 3:1); ir (CH_2Cl_2, cast): 3030, 1645, 1142, 1122, 1084, 1079, 1003, 941, 917, 733, 695 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.25 (5H, Ar-H), 5.28 (1H, d, 6 Hz, H-12), 5.21 (1H, s, H-14), 4.95 (1H, t, 2 Hz, H-19), 4.81 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.69 (1H, t, 2 Hz, H-19), 4.47 (1H, d, 12 Hz, Ar$\underline{CH_2}$O), 4.03-3.72 (4H, m), 2.85 (1H, d, 5.5 Hz, H-18), 2.46 (1H, d, 5.5 Hz, H-18), 2.55-2.34 (4H, m), 2.09 (1H, dd, 14.5, 6.75 Hz, H-11α), 1.84 (1H, dd, 12.5, 3.5 Hz, H-5), 1.69 (1H, dq, 13, 3.5 Hz, H-6α), 1.67 (1H, dd, 11.5, 6.5 Hz, H-9), 1.63 (1H, ddd, 11, 5.5, 2 Hz), 1.46 (1H, td, 13, 4 Hz, H-7α), 1.39 (1H, td, 13, 5.5 Hz), 1.08 (1H, dq, 13, 3.5 Hz, H-6β), 0.97 (3H, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ147.0 (s, C-3), 138.7 (s, Ar), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar), 106.2 (t, C-19), 105.4 (d, C-14), 104.5 (d, C-12), 84.3 (s, C-8), 69.4 (t), 66.1 (t), 64.7 (t), 59.6 (s, C-4), 57.9 (d, C-9), 52.2 (t, C-18), 50.4 (d, C-5), 39.6 (t), 38.3 (s, C-10), 35.1 (t), 31.4 (t), 29.9 (t), 19.2 (t), 13.5 (q, C-20); hrms: m/z calcd for $C_{25}H_{31}O_5$ ($M^+ - 1$): 411.2163; found: 411.2171(0.1), 339(33), 247(3), 91(100), 73(16).

(1S,5R,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-1,4-dimethyl-10-oxa-5-oxaspirotricyclo[7,4,0,$0^{9,13}$]tridecane **99**

The exocyclic olefin **98** (16.4 mg, 0.039 mmol), platinum oxide (1.4 mg), and 95% EtOH (2 mL) were mixed in a round-bottom flask. The system was purged with hydrogen three times. A balloon filled with hydrogen was fitted to the flask and the mixture stirred vigorously for 30 min. The solution was diluted with Et_2O and the catalyst removed by filtration. Evaporation of the solvent afforded **99** as a colorless oil (14.7 mg, 90%). Analysis of the ^{1}H nmr of the mixture shows that the α and β epimers at C-3 are present in a ratio of ca. 4:1 respectively. tlc: R_f 0.27 (dichloromethane/acetone, 96:4); ir (CH_2Cl_2, cast): 3030, 1454, 1142, 1122, 946, 735, and 698 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ7.37-7.23 (5H, m, Ar-H), 5.28 (1H, d, 6 Hz, H-12), 5.19 (1H, s, H-14), 4.82 (0.8H, d, 12 Hz, ArCH_2O-), 4.81 (0.2H, d, 12 Hz, ArCH_2O-), 4.49 (0.8H, d, 12 Hz, ArCH_2O-), 4.48 (0.2H, d, 12 Hz, ArCH_2O-), 4.02-3.76 (4H, m), 2.75 (0.8H, d, 4.5 Hz, H-18), 2.69 (0.2H, d, 4 Hz, H-18), 2.57 (0.2H, d, 4 Hz, H-18), 2.53 (0.8H, d, 4.5 Hz, H-18), 2.42-2.30 (2H, m), 2.12 (1H, dd, 14.5, 6.5 Hz, H-11α), 2.02-0.9 (10H, m), 1.10 (2.4H, d, 7 Hz, C-3 CH_3), 0.87 (2.4H, s, C-10 CH_3), 0.83 (0.6H, s, C-10 CH_3), 0.72 (0.6H, d, 6.5 Hz, C-3 CH_3); hrms: m/z calcd for $C_{22}\cancel{H_{29}}O_3$ ($M^+ - C_3H_5O_2$): 341.2109; found: 341.2116(29), 249(3), 149(3), 91(100), 73(61).

(1S,5R,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-5-hydroxy-10-oxa-1,4,5-trimethyltricyclo[7,4,0,0^{9,13}]-tridecane **100**

A 0.4 M solution of lithium triethylborohydride in THF (0.4 mL, 0.16 mmol) was added dropwise to a solution of the epoxide **99** (20.6 mg, 0.049 mmol) in dry THF (2 mL). After 30 min at room temperature the reaction was quenched with 10% NH_4Cl and diluted with Et_2O. The ethereal solution was washed with 10% NH_4Cl (2×), water (2×), brine (2×), dried ($MgSO_4$), and the solvent evaporated in vacuo to yield the alcohol **100** as a solid (18.4 mg, 90%). The ^1H nmr spectrum of the crude product displays the methyl groups for the C-3 β epimer (ca. 20% of the isomeric mixture) at δ0.95 (s, C-4 CH_3), δ0.91 (d, 7 Hz, C-3 CH_3), δ0.84 (s, C-10 CH_3). A pure sample of the C-3 α epimer was obtained by recrystallization from Skellysolve B/dichloromethane. m.p. 179-180°C; tlc: R_f 0.19 (Skellysolve B/ethyl acetate, 1:1), 0.27 (Skellysolve B/acetone, 7:3); ir (CH_2Cl_2, cast): 3530, 1450, 1080, 1002, 947, 935 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.23 (5H, m, Ar-H), 5.26 (1H, d, 6 Hz, H-12), 5.20 (1H, s, H-14), 4.82 (1H, d, 12 Hz, ArCH_2O-), 4.48 (1H, d, 12 Hz, ArCH_2O-), 4.04-3.76 (4H, m), 2.46 (1H, dt, 12, 3 Hz, H-7β), 2.34 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.07 (1H, dd, 14.5, 7 Hz, H-11α), 1.96 (1H, dq, 14, 3 Hz, H-6α), 1.92-1.78 (2H, m), 1.62 (1H, dd, 11.5, 7 Hz, H-9), 1.56 (1H, dd, 12.5, 2.5 Hz, H-5), 1.51 (1H, td, 12.5, 4 Hz, H-7α), 1.45-1.26 (3H, m), 1.17 (3H, s, C-4 CH_3), 1.14 (1H, m), 1.08 (1H, s, D_2O exchangeable), 1.01 (3H, d, 7 Hz, C-3 CH_3), 0.89 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ138.5 (s, Ar), 128.3 (d, Ar, 2×), 127.9 (d, Ar, 2×), 127.5 (s, Ar), 105.4 (d, C-14), 104.7 (d, C-12), 84.4 (s, C-8), 73.3 (s, C-4), 69.5 (t), 66.1 (t), 64.6 (t), 59.0 (d, C-9), 51.3 (d, C-5), 40.6 (d, C-3), 36.7 (s, C-10), 36.1 (t), 33.0 (t), 31.2 (t), 26.4 (t), 24.5 (q), 19.5 (t), 15.4 (q), 14.0 (q); hrms: m/z calcd for $C_{22}H_{31}O_3$ (M^+ - $C_3H_5O_2$): 343.2265; found: 343.2273(29), 251(2), 235(5), 135(2), 91(100), 73(22).

Mixture of olefins **101**

A solution of the C-3 α alcohol **100** (3.4 mg, 0.008 mmol) and p-toluenesulfonyl isocyanate (1 drop) in dry toluene (1 mL) was stirred at room temperature for 1 h under argon. The solution was refluxed for 1 1/2 h, then cooled to room temperature, and diluted with benzene. The reaction mixture was washed with water (2×), brine (2×), and dried ($MgSO_4$). The solvent was removed to yield the crude product which was purified by flash chromatography over silica gel (dichloromethane/acetone, 98:2) to give an oil (1.7 mg). The ^1H nmr spectrum of the product shows signals for two compounds in a ratio of 7:3. The exocyclic olefin is the major component of the mixture; tlc: R_f 0.56 (Skellysolve B/ethyl acetate, 1:1), 0.34 (dichloromethane/acetone, 98:2); ir (CH_2Cl_2, cast): 3070, 3030, 1643, 1454, 1122, 1073, 1007, 949, 935, 887, 733, 697 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.37-7.24 (5H, m,

Ar-H), 5.43 (0.3H, s, H-14), 5.28 (1H, d, 6 Hz, H-12), 5.21 (0.7H, s, H-14), 4.83 (0.7H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.81 (0.3H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.73 (0.7H, br s, H-18), 4.50 (0.7H, d, 12 Hz, Ar$\underline{CH_2}$O), 4.49 (0.3H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.40 (0.7H, t, 1.5 Hz, H-18), 4.04-3.77 (4H, m), 2.65 (0.3H, m), 2.53 (0.7H, dq, 7, 6 Hz, H-3), 2.48-1.22 (12H, m), 1.08 (2.1H, d, 7 Hz, C-3 CH_3), 0.99 (0.9H, d, 7 Hz, C-3 CH_3), 0.98 (0.9H, s, C-10 CH_3), 0.68 (2.1H, s, C-10 CH_3); hrms: m/z calcd for $C_{22}H_{29}O_2$ ($M^+ - C_3H_5O_2$): 325.216; found: 325.2167(31), 233(8), 205(1), 135(3), 91(100), 73(18).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) of one of the vinyl protons gave the following results: presaturation of the broad singlet at δ4.73: 26% (δ4.4, H-18) and 7% (δ2.53, H-3).

(1S,5S,6R,9R,11R,13R)-11-Benzyloxy-1,5-dimethyl-9-ethylenedioxymethyl-5-hydroxy-4-methylene-10-oxatricyclo[7,4,0,$0^{9,13}$]tridecane 102

A 0.4 M solution of lithium triethylborohydride in THF (0.2 mL, 0.08 mmol) was added dropwise to a solution of the allylic epoxide **98** (8.5 mg, 0.02 mmol) in dry THF (1 mL). The reaction mixture was stirred for 30 min at room temperature then quenched with 10% NH_4Cl and diluted with Et_2O. The ethereal solution was washed with 10%

NH_4Cl (2×), H_2O (2×), brine (2×), dried ($MgSO_4$), and the solvent removed *in vacuo* to give the allylic alcohol **102** as a colorless oil (7.5 mg, 90%); tlc: R_f 0.3 (Skellysolve B/acetone, 7:3); ir (CH_2Cl_2, cast): 3452, 1644, 1605, 1469, 1120, 1089, 941, 735, 697; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.27 (5H, m, Ar-H), 5.28 (1H, d, 6 Hz, H-12), 5.23 (1H, s, H-14), 5.01 (1H, br s, H-19), 4.79 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.72 (1H, br s, H-19), 4.45 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.05-3.77 (4H, m), 2.49-2.36 (2H, m), 2.35 (1H, ddd, 14.5, 11, 6 Hz, H-11β), 2.29 (1H, ddd, 14.5, 4, 2.75 Hz, H-6α), 2.11 (1H, m), 2.01 (1H, dd, 14.5, 7 Hz, H-11β), 1.59 (1H, dd, 11.5, 7 Hz, H-9), 1.56-1.21 (5H, m), 1.21 (1H, s, D_2O exchangeable), 1.17 (3H, s, C-4 CH_3), 0.97 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ156.5 (s, C-3), 138.7 (s, Ar), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar), 105.7 (t, C-19), 105.5 (d, C-14), 104.6 (d, C-12), 84.4 (s, C-8), 74.4 (s, C-4), 69.3 (t), 66.1 (t), 64.7 (t), 59.8 (d, C-9), 59.0 (d, C-5), 40.4 (t), 37.1 (s, C-10), 36.0 (t), 31.3 (t), 29.7 (t), 22.8 (q, C-18), 20.0 (t), 14.8 (q, C-20); hrms: m/z calcd for $C_{22}H_{29}O_3$ ($M^+ - C_3H_5O_2$): 341.2109; found: 341.2117(24), 373(1), 233(4), 193(2), 149(3), 91(100), 73(17).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) of the C-4 CH_3 gave the following results; presaturation of the singlet at δ1.17: 16%

(δ0.97, C-10 CH_3).

(1S,5S,6R,9R,11R,13R)-11-Benzyloxy-1,4-dimethyl-9-ethylenedioxymethyl-10-oxa-5-oxaspirotricyclo-[7,4,0,$0^{9,13}$]tridec-3-ene 103

The exocyclic olefin **98** (170 mg, 0.41 mmol), 10% palladium over activated carbon (17 mg), and acetonitrile (5 mL) were mixed in a round-bottom flask. The system was purged with hydrogen three times. A balloon filled with hydrogen was fitted to the flask and the slurry was stirred vigorously for 1 1/2 h. The catalyst was removed by filtration, and the solvent was removed to yield an oil (165 mg, 97% contaminated with less than 10% of **84**). A portion of the crude product was purified by flash chromatography over silica gel (dichloromethane/acetone, 48:2) to obtain a pure sample of **103**; tlc: R_f 0.33 (dichloromethane/acetone, 96:4), 0.31 (Skellysolve B/ethyl acetate, 3:2); ir (CH_2Cl_2, cast): 3020, 1453, 1143, 1120, 1084, 952, 736, 695 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.35-7.23 (5H, m, Ar-H), 5.61 (1H, m, H-2), 5.29 (1H, d, 6 Hz, H-12), 5.21 (1H, s, H-14), 4.81 (1H, d, 12 Hz, Ar$\underline{CH_2}$O), 4.48 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.04-3.76 (4H, m), 2.90 (1H, d, 4.5 Hz, H-18), 2.75 (1H, d, 4.5 Hz, H-18), 2.42-2.35 (1H, m), 2.40 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.12 (1H, dd, 14.5, 7 Hz, H-11α), 2.03 (1H, dd, 12.5, 3.5 Hz, H-5), 1.91 (1H, ddd, 17, 5, 1 Hz, H-1β), 1.68 (1H, dq, 14, 3.5 Hz, H-6α), 1.65 (1H, dd, 11.5, 7 Hz, H-9), 1.54-1.44 (2H, m), 1.47 (3H, br d, 1 Hz, C-3 CH_3), 1.15 (1H, dq, 13.5, 3.5 Hz, H-6β), 0.9 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ138.5 (s, Ar), 133.8 (s, C-3), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar), 126.3 (d, C-2), 104.9 (d, C-14), 104.5 (d, C-12), 84.0 (s, C-8), 69.4 (t), 66.1 (t), 64.7 (t), 59.2 (s, C-4), 57.1 (d, C-9), 47.1 (t, C-18), 46.6 (d, C-5), 41.3 (t), 37.1 (s, C-10), 34.9 (t), 31.3 (t), 19.7 (t), 15.6 (q), 14.4 (q); hrms: m/z calcd for $C_{25}H_{32}O_5$ (M^+): 412.2273; found: 412.2249(0.5), 339(27), 247(2), 119(4), 91(100), 73(26).

(1S,5S,6R,9R,11R,13R)-11-Benzyloxy-9-ethylenedioxymethyl-5-hydroxy-10-oxa-1,4,5-trimethyltricyclo[7,4,0,$0^{9,13}$]-tridec-3-ene 104

A 0.4 *M* solution of lithium triethylborohydride in THF (3.5 mL, 1.4 mmol) was added dropwise to a solution of the allylic epoxide **103** (165 mg, 0.4 mmol) in dry THF (5 mL) at 0°C. The reaction mixture was stirred for 30 min at 0°C, then quenched with 10% NH_4Cl and diluted with Et_2O. The ethereal solution was washed with 10% NH_4Cl (2×), H_2O (2×), brine (2×), and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the allylic alcohol **104** as a colorless oil (155.6 mg, 93%); tlc: R_f 0.39

(dichloromethane/acetone, 4:1), 0.39 (ethyl acetate/Skellysolve B, 7:3); ir (CH_2Cl_2, cast): 3400, 1453, 1142, 1121, 1086, 1035, 949, 936, 736, 697 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ7.34-7.22 (5H, m, Ar-H), 5.33 (1H, br d, 6 Hz, H-2), 5.27 (1H, d, 6 Hz, H-12), 5.25 (1H, s, H-14), 4.81 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.47 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.05-3.76 (4H, m), 2.46 (1H, d, 9, 3 Hz, H-7β), 2.38 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.07 (1H, dd, 14.5, 7 Hz, H-11α), 2.03 (1H, dq, 14, 3 Hz, H-6α), 1.92 (1H, br d, 16.5 Hz, H-1α), 1.77 (1H, dd, 16.5, 5 Hz, H-1β), 1.74 (3H, br d, 1.5 Hz, C-3 CH_3), 1.64-1.45 (3H, m), 1.58 (1H, dd, 11.5, 7 Hz, H-9), 1.15 (3H, s, C-4 CH_3), 1.06 (1H, s, D_2O exchangeable), 0.86 (3H, s, C-10 CH_3); ^{13}C nmr ($CDCl_3$): δ138.8 (s, Ar), 128.3 (d, Ar, 2×), 127.8 (d, Ar, 2×), 127.4 (d, Ar), 123.8 (s, C-3), 121.9 (d, C-2), 105.1 (d, C-14), 104.5 (d, C-12), 84.1 (s, C-8), 72.6 (s, C-4), 69.3 (t), 66.1 (t), 64.7 (t), 57.7 (d, C-9), 56.1 (d, C-5), 41.4, 36.3, 35.8, 31.2, 20.9, 20.2 (q), 17.0 (q), 15.8 (q); hrms: m/z calcd for $C_{22}H_{29}O_3$ ($M^+ - C_3H_5O_2$): 341.2109; found: 341.2117(27), 323(13), 233(6), 215(4), 133(9), 91(100), 73(22).

Formation of the alcohols **100** from **104**

The allylic alcohol **104** (35 mg, 0.084 mmol), 10% palladium on activated carbon (15 mg), and Et_2O (10 mL) were mixed in a hydrogenation flask. The system was purged with hydrogen three times. The flask was shaken under 3 atmospheres of hydrogen for 32 h. Then the catalyst was removed by filtration and the solvent evaporated to give the alcohol **100** as a colorless oil (32 mg, 91%). Analysis of the ^{1}H nmr of the mixture shows that the α and β epimers at C-3 are present in a ratio of 1:8 respectively; tlc: R_f 0.32 (dichloromethane/acetone, 4:1), 0.33 (ethyl acetate/Skellysolve B, 7:3); ir (CH_2Cl_2, cast): 3470, 1455, 1143, 1122, 1097, 1077, 948, 735, 695 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ7.36-7.28 (5H, Ar-H), 5.26 (1H, d, 6 Hz, H-12), 5.22 (1H, s, H-14), 4.82 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.48 (1H, d, 12 Hz, Ar$\underline{CH_2}$O-), 4.05-3.77 (4H, m), 2.45 (1H, dt, 12, 3 Hz, H-7β), 2.35 (1H, ddd, 14.5, 11.5, 6 Hz, H-11β), 2.36-2.32 (1H, m, D_2O exchangeable), 2.12-1.94 (2H, m), 2.04 (1H, dd, 14.5, 7 Hz, H-11α), 1.60 (1H, dd, 11.5, 7 Hz, H-9), 1.67-1.19 (7H, m), 0.93 (3H, s, C-4 CH_3), 0.90 (3H, d, 7 Hz, C-3 CH_3), 0.84 (3H, s, C-10 CH_3); hrms: m/z calcd for $C_{22}H_{31}O_3$ (M^+ - $C_3H_5O_2$): 343.2265; found: 343.2273(27), 251(2), 235(7), 135(2), 133(2), 91(100), 73(28).

REFERENCES

1. J. Meinwald, M.P. Bosch, F. Camps, J. Coll, A. Guerrero, T. Fatsuoka, J. Org. Chem. **51**, 773 (1986) and references cited therein.
2. I. Kubo, K. Nakanishi, Y.W. Lee, M. Pettei, F. Pilkiewicz, J. Chem. Soc. Chem. Commun., 1013 (1976).
3. a) I. Kubo, K. Nakanishi, Y.W. Lee, M. Pettei, F. Pilkiewicz, I. Miura, Tet. Lett, 4553 (1977); b) F.S. El-Feraly, A.T. McPhail, K.D. Onan, J. Chem. Soc., Chem. Commun., 75 (1978).
4. C.S. Barnes, J.W. Loder, Austral. J. Chem., **15**, 322 (1962).
5. L. Canonica, A. Corbella, G. Jommi, J. Krepinsky, Tet. Lett., 2137 (1967).
6. K. Nakanishi, I. Kubo, Isr. J. Chem., **16**, 28 (1977).
7. I. Kubo, I. Ganjian, Experientia, **37**, 1063 (1981).
8. M. Ohno, A. Okanara, H. Nakai, Tet. Lett., **23**, 1087 (1982).
9. K. Nakanishi, S.P. Tanis, J. Am. Chem. Soc., **101**, 4398 (1979).
10. S.V. Ley, D.M. Hollinshead, S.C. Howell, M. Mahon, N.M. Ratcliffe, J. Chem. Soc., Perkin Trans 1, 1579 (1983).

11. T. Oishi, T. Nakata, A. Akita, T. Naito, Chem. Pharm. Bull., **28**, 2172 (1980).

12. a) A.S. Kende, T.J. Blacklock, Tet. Lett., **21**, 3119 (1980); b) D.J. Goldsmith, H.S. Kezar, Tet. Lett, **21**, 3453 (1980).

13. P.A. Wender, S.L. Eck, Tet. Lett., **23**, 1871 (1982).

14. W.A. Ayer, C.E. MacDonald, G.G. Iverach, Tet. Lett., 1095 (1963).

15. W.A. Ayer, P.D. Deshpande, Can. J. Chem., **51**, 77, 2323 (1973).

16. P.F. Zinkel, CHEMTECH., 235 (1975).

17. N.J. de Souza, S.V. Bhat, B.S. Baswa, H. Dornauer, H.W. Fehlhaber, Tet. Lett., 1669 (1977).

18. G.W. Hedrick, W.D. Lloyd, Org. Synth., **45**, 64 (1965).

19. R.V. Lawrence, R.N. Moore, J. Am. Chem. Soc., **80**, 1438 (1958).

20. W.A. Ayer, C.E. MacDonald, J.B. Stothers, Can. J. Chem., **41**, 1113 (1963).

21. J.J. Pappas, W.P. Keaveney, E. Gancher, M. Berger, Tet. Lett., 4273 (1966).

22. W.A. Adam, I. Erden, Angew Chem., Int. Ed., **17**, 210 (1978); W.A. Adam, I. Erden, J. Org. Chem., **43**, 2737 (1978).

23. R.M. Silverstein, G.C. Bassuer, T.C. Morrill, **Spectroscopic Identification of Organic Compounds**, 4th ed., John Wiley and Sons, 1981.

24. K. Nakanishi, P.H. Solomon, **Infrared Absorption Spectroscopy**, 2nd ed., Holden-Day Inc., Oakland, 1977, p. 40.

25. L.M. Jackman, S. Sternhell, **Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry**, 2nd ed., Pergamon Press, New york, 1969, p 184.

26. R.U. Lemieux, W.S. Johnson, R. Pappo, D.S. Allen, J. Org. Chem., **21**, 478 (1956).

27. J.S. Baran, J. Org. Chem., **25**, 257 (1960).

28. N.L. Wendler, H.C. Slates, J. Am. Chem. Soc., **81**, 5472 (1959).

29. K.B. Sharpless, H.J. Carlsen, T. Katsuki, V.S. Martin, J. Org. Chem., **46**, 3936 (1981).

30. J.L. Luche, J. Am. Chem. Soc., **100**, 2226 (1978).

31. Reference 25, p. 280.

32. C.A. Grob, Angew. Chem. Int. Ed., **8**, 535 (1969).

33. E.E. van Tamelen, M. Shamma, A.W. Burgstahler, J. Wolinsky, R. Tamm, P.E. Aldrich, J. Am. Chem. Soc., **91**, 7315 (1969).

34. E.M. Burgess, H.R. Penton, E.A. Taylor, J. Org. Chem., **38**, 26 (1973).

35. K.L. Servis, R.K. Crossland, J. Org. Chem., **35**, 3195 (1970).

36. Reference 25, p. 80.

37. B. Glatz, G. Helmchen, H. Muxfedt, H. Porcaer, R. Preno, J. Senn, J.J. Stezowski, R.J. Stouda, D.R. White, J. Am. Chem. Soc., **101**, 2171 (1979).

38. Reference 24, p. 50.

39. S. Hanessian, N.R. Plessas, J. Chem. Soc., Chem. Commun., 706 (1968).

40. B.M. Trost, Acc. Chem. Res., **11**, 453 (1978); J. Nokami, K. Veta, R. Okawara, Tet. Lett., 4903 (1978); D.J. Cram, C.A. Kingsbury, J. Am. Chem. Soc., **82**, 1810 (1960).

41. D.H.R. Barton, I. Ager, G. Lucente, P.G. Sammes, J. Chem. Soc., Chem. Commun., 601 (1972); P.G. Cooper, L.D. Hatfield, J. Fisher, F.L. Jose, Tet. Lett., 4897 (1970).

42. E.J. Corey, R.A. Sneen, J. Am. Chem. Soc., **77**, 2505 (1955).

43. L.F. Fieser, M. Fieser, **Steroids**, Reinhold, New York, 1959, p. 276.

44. Y. Asakawa, M. Toyota, T. Aratani, Tet. Lett., 1407 (1977).

45. F. Johnson, Chem. Rev., **68**, 375 (1968).

46. J.Y. Lallemand, D. Guillerm, M. Delarve, M. Jalali-Naini, P. Lemaitre, Tet. Lett., 1043 (1984).

47. E. Vedejs, D.A. Engller, J.E. Telscaow, J. Org. Chem., **43**, 188 (1978).

48. A. Ohsuka, A. Matsukawa, Chem. Lett., 635 (1979).

49. E.J. Corey, J.W. Suggs, Tet. Lett., 2647 (1975).

50. J. March, **Advanced Organic Chemistry**, 3rd ed., John Wiley and Sons Inc., New York, 1985, p. 1096.

51. Huang-Minlon, J. Am. Chem. Soc., **68**, 2487 (1946); Huang-Minlon, J. Am. Chem. Soc., **71**, 3301 (1949).

52. Reference 24, p. 16.

53. D.H.R. Barton, R.E. O'Brien, S. Sternhell, J. Chem. Soc., 470 (1962).

54. H.B. Henbest, M.F. Grundon, M.D. Scott, J. Chem. Soc., 1855 (1963).

55. D.J. Cram, M.R.V. Sahyun, G.R. Knox, J. Am. Chem. Soc., **84**, 1734 (1962).

56. Reference 24, pp. 33 and 50.

57. L. Caglioti, Tetrahedron, **22**, 487 (1966).

58. G.W. Kabalka, S.T. Summers, J. Org. Chem., **46**, 1217 (1981).

59. G.W. Kabalka, J.H. Chandler, Synth. Commun., **9**, 275 (1979).

60. G.W. Kabalka, J.D. Baker, J. Org. Chem., **40**, 1834 (1975).

61. W. Herz, H. Grisebach, G.W. Kirby, **Progress in the Chemistry of Organic Natural Products**, Vol. 36, Wien-Springer-Verlag, New York, 1979.

62. a) W. Hartwig, Tetrahedron, **39**, 2609 (1983); b) D.H.R. Barton, W.B. Motherwell, A. Stange, Synthesis, 743 (1981).

63. R.W. Holder, M.G. Matturro, J. Org. Chem., **42**, 2166 (1977).

64. H.C. Brown, S. Krishnamurthy, J. Org. Chem., **41**, 3064 (1976).

65. D.H. Hua, G. Sinai-Zingde, S. Venkataraman, J. Am. Chem. Soc., **107**, 4088 (1985).

66. T.B. Johnson, I.B. Douglass, J. Am. Chem. Soc., **60**, 1486 (1938).

67. H.V. Siemann, G. Langbein, M. Meyer, Pharmazie, **33**, 706 (1978).

68. P.G. Gassman, W.N. Schenk, J. Org. Chem., **42**, 918 (1977).

69. H.H. Zeiss, W.B. Martin, J. Am. Chem. Soc., **75**, 5935 (1953); E.E. van Tamelen, E.G. Taylor, J. Am. Chem. Soc., **102**, 1202 (1980).

70. T. Matsumoto, S. Imai, H. Kawashima, M. Mitsuki, Bull. Chem. Soc. Jpn., **54**, 2099 (1981).

71. C.S. Swindell, S.F. Pritcher, J. Org. Chem., **51**, 793 (1986).

72. J.K. Crandall, M. Apparu, Org. React. (N.Y.), **29**, 345 (1983).

73. E.J. Corey, A. Marfat, J.R. Falck, J.O. Albright, J. Am. Chem. Soc., **102**, 1433 (1980).

74. A. Nickon, R.W. Denny, Org. React. (N.Y.), **20**, 133 (1973).

75. L. Lombardo, Tet. Lett., **25**, 227 (1984).

76. G.H. Posner, Org. React. (N.Y.), **22**, 253 (1975).

77. B.H. Lipshutz, R.S. Wilhelm, J.A. Kozlowski, D. Parker, J. Org. Chem., **49**, 3928 (1984); B.H. Lipshutz, J.A. Kozlowski, R.S. Wilhelm, J. Am. Chem. Soc., **104**, 2305 (1982).

78. G. Linstrumelle, C. Huynh, F. Perguini-Boumechal, Tet. Lett., 1503 (1979).

79. F. Camps, J. Coll, A. Parente, Synthesis, 215 (1978).

80. K.B. Sharpless, M.A. Umbreit, J. Am. Chem. Soc., **99**, 5526 (1977).

81. Reference 50, p. 920.

82. D. Swern, A.J. Mancuso, S.L. Huang, J. Org. Chem., **43**, 2480 (1978).

83. C.H. Heathcock, J.E. Ellis, J.S. Dutcher, J. Org. Chem., **41**, 2670 (1976).

84. J.M. Conia, J.C. Limassel, Bull. Soc. Chim., 1936 (1967).

85. W.H. Daly, L.C. Roach, J. Chem. Soc., Chem. Commun., 606 (1970).

86. T.R.B. Mitchell, J. Chem. Soc. (B), 823 (1970).

87. H.O. House, **Modern Synthetic Reactions**, 2nd ed., W.A. Benjamin, Menlo Park, CA, 1972, p. 22.

88. W.G. Kofrom, L.M. Baclawski, J. Org. Chem., **41**, 1879 (1976).

89. W.C. Still, M. Kahn, A. Mitra, J. Org. Chem., **43**, 2923 (1978).

90. D.L. Rabenstein, T.T. Nakashima, D.W. Brown, J. Mag. Res., **45**, 302 (1981).